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(54) **Title:** CAPSAICIN RECEPTOR LIGANDS

(57) **Abstract:** Disclosed are diaryl piperazines and related compounds. These compounds are selective modulators of capsaicin receptors, including human capsaicin receptors, that are, therefore, useful in the treatment of a chronic and acute pain conditions, itch and urinary incontinence. Methods of treatment of such disorders and well as packaged pharmaceutical compositions are also provided. Compounds of the invention are also useful as probes for the localization of capsaicin receptors and as standards in assays for capsaicin receptor binding and capsaicin receptor mediated cation conductance. Methods of using the compounds in receptor localization studies are given.

CAPSAICIN RECEPTOR LIGANDS

Field of the Invention

This invention relates compounds that bind with high selectivity and high affinity to Vanilloid Receptors, especially Type I Vanilloid Receptors, also known as capsaicin receptors or VR1 Receptors. In an important aspect the invention provides capsaicin receptor, preferably human VR1 receptor, antagonists that are not capsaicin analogs (e.g., they do not contain a phenyl ring with two oxygen atoms bound to two adjacent ring carbons), are free of agonist activity, and exhibit an unprecedented level of affinity for the VR1 receptor. In another aspect, the invention provides aryl piperazines and related compounds that act as VR1 receptor ligands. In addition, this invention relates to such VR1 receptor ligands, high affinity antagonists and pharmaceutical compositions comprising such compounds and to the use of such compounds in treatment of diseases and other health-related conditions. Additionally this invention relates to the use of aryl piperazines and related compounds as tool for the analysis of VR1 receptors and as probes for the quantitative measurement and localization of VR1 receptors in cell and tissue samples.

Background

The sensation of pain can be triggered by any number of physical or chemical stimuli. In mammals, the peripheral terminals of a group of specialized small diameter sensory neurons, termed "nociceptors" mediate this response to a potentially harmful stimulus.

In efforts to discover better analgesics for the treatment of both acute and chronic pain, and to develop treatments for various neuropathic pain states, considerable research has been

focused on the molecular mechanism of nociception. The response to heat, low extracellular pH (acidity), or capsaicin (the compound responsible for the hotness of hot peppers) is characterized by the persistent activation of nociceptors. It has been shown that both heat and capsaicin are capable of activating dorsal root ganglion and trigeminal ganglion neurons via an influx of cations. Additionally, moderately acidic conditions produce this response and can also potentiate the response of nociceptors to heat and capsaicin.

Capsaicin responses in isolated sensory neurons show dose-dependence and are also evoked by structural analogues of capsaicin that share a common vanilloid moiety. The term vanilloid receptor (VR) was coined to describe the neuronal membrane recognition site for capsaicin and such related irritant compounds. It was postulated that the VR is a nonselective cation channel with a preference for calcium. In 1989, resiniferatoxin (RTX), a natural product of certain *Euphorbia* plants, was recognized as an ultrapotent VR agonist. Specific binding of 3 H RTX provided the first unequivocal proof for the existence of a vanilloid receptor. The capsaicin response is competitively inhibited (and thereby antagonized) by another capsaicin analog, capsazepine and is also inhibited by the non-selective cation channel blocker ruthenium red. These antagonists bind to VR with no more than moderate affinity (i.e., with K_i values of no lower than 140 uM).

Interest in characterizing VRs led to the cloning of a functional rat capsaicin receptor (VR1), from a rat dorsal root ganglion cDNA library. A human version of VR1 has also been described, and the term VR1 is used herein to refer to either or both.

The capsaicin receptor's channel opens in response to elevated temperatures (higher than about 45°C). Capsaicin and related compounds, as well as protons are stimuli that lower the threshold channel opening, so that in the presence of any of these stimuli the capsaicin receptor can be opened even at room temperature.

Opening of the capsaicin receptor channel is followed by the release of inflammatory peptides from neurons expressing the receptor and other nearby neurons, increasing the pain response. After initial activation by capsaicin the capsaicin receptor undergoes a rapid desensitization, possibly via phosphorylation of intracellular sites of the receptor. Capsaicin and related VR1 agonist vanilloid compounds have enjoyed long pharmaceutical use as topical anaesthetics. While such compounds initially cause a strong burning sensation, receptor desensitization provides pain relief.

Localization of the capsaicin receptor in the dorsal root ganglion established this receptor as a leading target for analgesic discovery. Most currently marketed analgesic compounds act centrally, and often have side effects. Analgesic compounds that act peripherally are desirable for treating acute and chronic pain more effectively and with fewer side effects. Thus, compounds that interact with the capsaicin receptors, particularly antagonists of this receptor, which would not elicit the initial painful sensation of currently marketed capsaicin containing compounds, are desirable for the treatment of chronic and acute pain, itch, and urinary incontinence.

Description of Related Art

The vanilloid compounds capsaicin and Resiniferatoxin (RTX) act as potent and specific agonists of the capsaicin

receptor. Capsazepine (which contains a phenyl ring with two oxygen atoms bound to two adjacent ring carbons and is therefore a capsaicin analog) acts as a moderate affinity competitive capsaicin receptor antagonist. Iodo-RTX is a capsaicin analog that has recently been reported to act as a high affinity antagonist. The inorganic dye, Ruthenium red, also antagonizes capsaicin responses of the receptor, albeit as a non-selective cation channel blocker. For an extensive review of vanilloid receptor ligands see Szallasi and Blumberg, (Pharmacological Reviews (1999) 51(3): 159-211).

Summary of the Invention

This invention relates to VR1 receptor ligands, particularly VR1 receptor antagonists, and methods of using VR1 receptor antagonists for the treatment of neuropathic pain, peripheral-nerve-mediated pain, and pain, inflammatory and broncho-constriction symptoms resulting from exposure to capsacin-receptor-activating stimuli such as capsaicin and tear gas.

In one aspect the invention provides novel chemical compounds that act as capsaicin receptor modulatory agents, some of which exhibit antagonist potency greater than that of any previously described VR1 receptor antagonist. Compounds that act as capsaicin receptor antagonists and bind to capsaicin (preferably human VR1) receptors with K_i values of less than 100uM, as measured by a capsacin receptor binding assay, such as the assay given by Example 10, or that inhibit capsaicin activity in an assay for determination of capsaicin receptor antagonist effects (Example 11) with EC_{50} values of less than or equal to 100uM, are referred to herein as potent capsaicin receptor antagonists; such compounds that bind or antagonize with K_i or EC_{50} values of less than or equal to 10uM

are referred to herein as highly potent capsaicin receptor antagonists.

In an additional aspect, the invention provides methods of using the potent capsaicin receptor antagonist compounds of the invention for the treatment of symptoms resulting from exposure to painful capsaicin receptor activating stimuli. In particular, the invention provides methods of treating subjects who have been exposed to capsaicin or have been burnt by heat, light, tear gas, or acid exposure, the methods comprising administering to such subjects an effective amount of a potent capsaicin receptor antagonist, preferably a highly potent (high potency) capsaicin receptor antagonist, so that the subject's symptoms of pain or sensitivity are reduced. Preferred compounds of the invention provide pain relief without loss of consciousness, and preferably without sedation, in such subjects that is equal to or grater than the degree of pain relief that can be provided to such subjects by morphine without loss of consciousness. Highly preferred compounds provide such pain relief while causing only transient (i.e., lasting for no more than one half the time that pain relief lasts) or no sedation (see Example 16 for sedation assay). Subjects or patients referred to herein may be humans or non-human mammals including domestic companion animals (pets) and livestock animals, as discussed more fully below.

In yet another aspect the invention provides methods of treating of neuropathic pain based on the unexpected finding that capsaicin receptor antagonists can alleviate such pain.

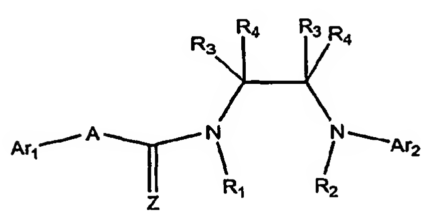
This invention also provides aryl piperazines and related compounds that bind with high affinity and high selectivity to capsaicin receptors, including human capsaicin receptors, also known as VR1 receptors.

Thus, the invention provides novel compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, or Formula VII, Formula VIII, Formula IX and Formulae A-F shown below (the "compounds of the invention," hereinafter Formulae I-IX and Formulae A-F), and pharmaceutical compositions comprising compounds of Formulae I-IX and Formulae A-F.

The invention further comprises methods of treating patients suffering from certain diseases or conditions, especially those involving pain or urinary incontinence, with an amount of a compound Formulae I-IX and Formulae A-F that is effective to improve the symptoms (e.g., reduce pain or reduce the frequency of urinary incontinence) of the disease or condition being treated.

Additionally this invention relates to the use of the compounds of the invention as reagents, standards, and probes for measurement, characterization and localization of capsaicin receptors, particularly VR1 receptors (e.g., in cells or tissues.

Accordingly, a broad aspect of the invention is directed to compounds of Formula I:



Formula I

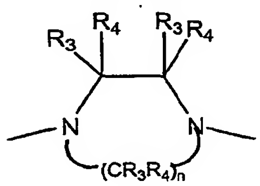
or the pharmaceutically acceptable salts thereof, wherein:

A is chosen from O, S, NR_A, CR_BR_B', $NR_ACR_BR_B'$, $CR_BR_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen or alkyl;

Z is oxygen or sulfur;

R_1 and R_2 independently represent hydrogen or lower alkyl; or

R_1 and R_2 are taken together to form a 5 to 8 membered nitrogen containing ring of the formula:



wherein n is 1, 2, or 3;

R_3 and R_4 are independently selected at each occurrence from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted -S(O)$_n$NHalkyl; optionally substituted -S(O)$_n$N(alkyl)(alkyl); optionally substituted -NHC(=O)alkyl; optionally substituted -NC(=O)(alkyl)(alkyl); optionally substituted -NHS(O)$_n$alkyl; optionally substituted -NS(O)$_n$(alkyl)(alkyl); optionally substituted saturated or partially unsaturated heterocycloalkyl of from 5 to 8 atoms, which saturated or partially unsaturated heterocycloalkyl contains 1, 2, or 3 heteroatoms selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; or optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least

one of said rings, from 1 to about 3 heteroatoms per ring selected from the group consisting of N, O, and S;

or any two

R_3 and R_4 not attached to the same carbon may be joined to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms selected from N, O, and S; and

Ar_1 and Ar_2 are the same or different and independently represent optionally substituted cycloalkyl; an optionally substituted heterocycloalkyl ring of from 5 to 8 atoms, which heterocyloalkyl ring contains 1, 2, or 3 heteroatoms selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; or optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring selected from the group consisting of N, O, and S, and

n is independently chosen at each occurrence from 0, 1, and 2.

In specific embodiments of the invention R_1 and R_2 are joined to form a 5 to 7-membered heterocycloalkyl ring, e.g. R_1 and R_2 may be joined to form a piperazine ring. This 5 to 7-membered heterocycloalkyl ring is preferably unsubstituted or substituted at one or two positions with a C_{1-6} alkyl group, such as methyl or ethyl. The variable "Z" is preferably oxygen and the variable "A" is generally NH, CH=CH, or CH_2NH. Ar_1 and Ar_2 are preferably optionally substituted phenyl or optionally

substituted pyridyl; optionally substituted 2-pyridyl is preferred for Ar_2. Substitutuents that may occur on Ar_1 and Ar_2 include, but are not limited to, butyl, isopropyl, trifluoromethyl, nitro, methyl, and halogen. Substitution at the 4 position of Ar_1 (when Ar_1 is phenyl or pyridyl) and substitution at the 3 position of Ar_2 (when Ar_2 is phenyl or pyridyl) are described in specific embodiments of the invention.

Detailed Description of the Invention

The invention is particularly directed to compounds of Formula I, in which R_1 and R_2 independently represent hydrogen or lower alkyl, e.g., C_{1-6} alkyl. Such compound will be referred to as compounds of Formula IA.

Preferred compounds and pharmaceutically acceptable salts of Formula IA are those wherein:

R_3 and R_4 are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, haloalkyl, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6, alkenyl substituted with 0-2 R_6; alkynyl substituted with 0-2 R_6; alkoxy substituted with 0-2 R_6, -NH(alkyl) substituted with 0-2 R_6, -N(alkyl)(alkyl) where each alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y;

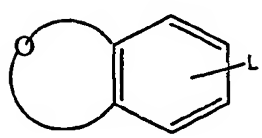
or any two

R_3 and R_4 not attached to the same carbon may be joined to form an aryl ring substituted with 0-3 R_6, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R_6, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which

heterocyclic ring is substituted with 0-2 R_6 and contains 1, 2, or 3 heteroatoms selected from N, O, and S; and

Ar_1 and Ar_2 may be the same or different and are selected from the group consisting of cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R_5; or

Ar_1 and Ar_2 may be the same or different and represent a bicyclic oxygen-containing group of the formula:



optionally mono-, di-, or trisubstituted with R_5, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R_5 is independently selected at each occurrence from the group consisting of halogen, cyano, nitro, haloalkyl, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6, alkenyl substituted with 0-2 R_6, alkynyl substituted with 0-2 R_6, alkoxy substituted with 0-2 R_6, -NH(alkyl) substituted with 0-2 R_6, -N(alkyl)(alkyl) where each alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, alkyl, alkoxy, -NH(alkyl), -N(alkyl)(alkyl), -S(O)$_n$(alkyl), haloalkyl, haloalkoxy, CO(alkyl), CONH(alkyl), CON(alkyl$_1$)(alkyl$_2$) where alkyl$_1$ and alkyl$_2$ may be joined to form a heterocycloalkyl ring of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms selected from N, O, and S, -XR$_7$, and Y;

X is independently selected at each occurrence from the group consisting of -CH$_2$-, -CHR$_8$-, -O-, -S(O)$_n$-, -NH-, -NR$_8$-, -C(=O)-, -C(=O)O-, -C(=O)NH-, -C(=O)NR$_8$-, -S(O)$_n$NH-, -S(O)$_n$NR$_8$-, NHC(=O)-, -NR$_8$C(=O)-, -NHS(O)$_n$-, and -NR$_8$S(O)$_n$-;

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -NHS(O)$_n$(alkyl), -S(O)$_n$(alkyl), -S(O)$_n$NH(alkyl), -S(O)$_n$N(alkyl$_3$)(alkyl$_4$) where alkyl$_3$ and alkyl$_4$ may be joined to form a heterocycloalkyl ring consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms selected from N, O, and S, and Y';

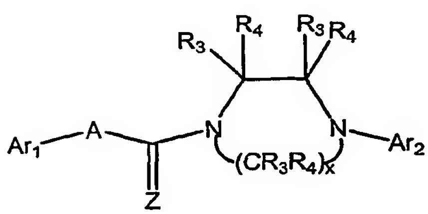
Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further

substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to 8-memberered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2. Such compounds and pharmaceutically acceptable salts thereof, will be referred to as compounds of Formula IB.

The invention is further directed to compounds of Formula II



Formula II

and the pharmaceutically acceptable salts thereof, wherein:

A, Z, R_3, R_4 are as defined for Formula I or for Formula IB;

Ar_1 and Ar_2 are as defined for Formula I or for formula IB; and

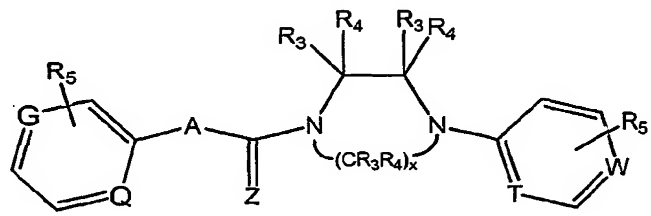
x is 1 or 3.

Preferred compounds and salts of Formula II are those in which .

R_A, R_B, and R_B' (which are contained in the definition of A) are independently selected at each occurrence from hydrogen or C_{1-6}alkyl.

Other preferred compounds salts of Formula II are those in which Z is oxygen, and those in which Z is oxygen and A is NH.

The invention is further directed to compounds of Formula III



Formula III

and the pharmaceutically acceptable salts thereof, wherein:

G, Q, T, and W are the same or different and represent N, CH, or CR_5, where R_5 is as defined for Formula IB;

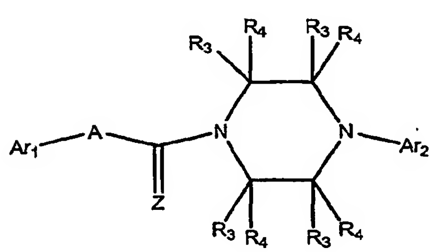
R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen or C_{1-6}alkyl;

Z is oxygen or sulfur;

R_3 and R_4 are as defined for Formula I or for Formula IB; and

x is 1 or 3.

The invention also included compounds of Formula IV



Formula IV

and the pharmaceutically acceptable salts thereof, wherein:

Z is S or O (preferably O);

A, R_3, and R_4 is as defined for Formula I or Formula IB;

Ar_1 and Ar_2 may be the same or different and are selected from the group consisting of cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl; wherein Ar_1 is optionally mono-, di-, or trisubstituted with R_5, and Ar_2 is optionally mono-, di-, or trisubstituted with R_9; or

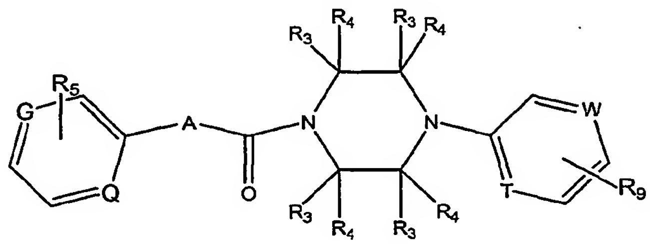
Ar_1 and Ar_2 may be the same or different and represent a bicyclic oxygen-containing group as described for Formula IB,

R_5 is independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6, alkenyl substituted with 0-2 R_6, alkynyl substituted with 0-2 R_6, alkoxy substituted with 0-2 R_6, -NH(alkyl) substituted with 0-2 R_6, -N(alkyl)(alkyl) where each alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y;

R_9 is independently selected at each occurrence from the group consisting of cyano, nitro, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6, alkenyl substituted with 0-2 R_6, alkynyl substituted with 0-2 R_6, alkoxy substituted with 0-2 R_6, -NH(alkyl) substituted with 0-2 R_6, -N(alkyl)(alkyl) where each alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y; and

R_6, R_7, R_8, X, Y and Y' are as defined for Formula IB.

Another embodiment of the invention is directed to compounds of Formula V



Formula V

and the pharmaceutically acceptable salt thereof, wherein:

G, Q, T, and W are the same or different and are selected from the group consisting of N, CH, and CR_5, wherein T or W or both is N;

A, R_3, and R_4 are as defined for Formula I or for Formula IB (preferably A is -CH=CH-, $-CH_2NH$, NH, and R_3 and R_4 are hydrogen or C_{1-6} alkyl);

Z is oxygen or sulfur (preferably oxygen);

R_5 represents 1 to 3 substituents and is independently selected at each occurrence from the group consisting of cyano, hydroxy, amino, C_{3-6} alkyl substituted with 0-2 R_6, C_{2-6} alkenyl substituted with 0-2 R_6, C_{2-6} alkynyl substituted with 0-2 R_6, C_{3-6} alkoxy substituted with 0-2 R_6, $-NH(C_{1-6}alkyl)$ substituted with 0-2 R_6, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y;

R_9 represents 0 to 3 substituents and is independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, $-NH(C_{1-6}alkyl)$

substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6, $-XR_7$, and Y;

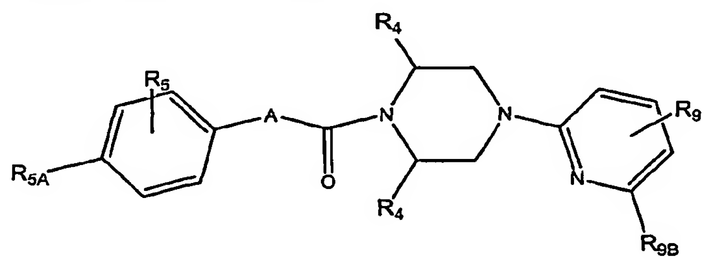
R_6, R_7, R_8, X, Y, and Y′ are as defined for Formula IB.

The invention is particularly directed to compounds and salts of Formula V wherein G and Q are selected from the group consisting of CH and CR_5.

The invention is also directed to compounds and salts of Formula V wherein G , Q, and W are independently selected at each occurrence from the group consisting of CH and CR_5; and T is N.

For compounds of Formula V, particularly preferred R_6 substituents are halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, -NH(C_{1-4}alkyl), and -N(C_{1-4} alkyl)(C_{1-4} alkyl).

Still another embodiment of the invention is directed of compounds of Formula VI



Formula VI

and the pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and CH_2NH;

R_4 is independently chosen from hydrogen and C_{1-4} alkyl;

R_5 represents 0 to 2 substituents and is independently chosen at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl

substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6;

R_9 represents 0 to 2 substituents and is independently chosen at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, and -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6;

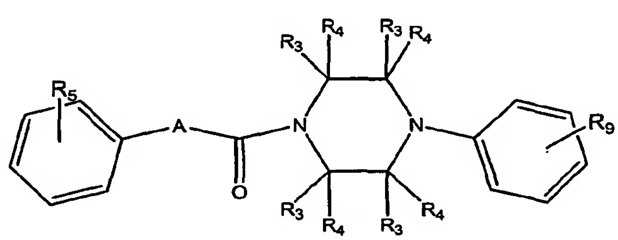
R_{5A} is independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), and

-N(C_{1-6} alkyl)(C_{1-6} alkyl);

R_{9B} is independently selected from the group consisting of halogen, nitro, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), and -N(C_{1-6} alkyl)(C_{1-6} alkyl); and

R_6 is independently selected at each occurrence the group consisting of halogen, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -NH(C_{1-4} alkyl), and -N(C_{1-4} alkyl)(C_{1-4} alkyl).

The invention is also directed to compounds of Formula VII



Formula VII

and the pharmaceutically acceptable salts thereof, wherein:

A, R_3, and R_4 are as defined for Formula I or for Formula IB;

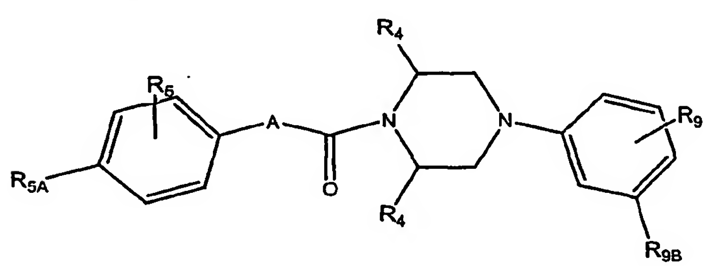
R_5 is independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, C_{1-6} alkyl substituted with 0-2 R_6, C_{2-6} alkenyl substituted with 0-2 R_6, C_{2-6} alkynyl substituted with 0-2 R_6, C_{1-6} alkoxy substituted with 0-2 R_6, -NH(C_{1-6} alkyl) substituted with 0-2 R_6, -N(C_{1-6} alkyl)(C_{1-6} alkyl) where each alkyl is independently substituted with 0-2 R_6, -XR_7, and Y;

R_9 represents 0-3 substituents and is independently selected at each occurrence from the group consisting of bromo, haloalkyl, haloalkoxy, hydroxy, C_{2-6} alkyl substituted with 0-2 R_6, C_{2-6} alkenyl substituted with 0-2 R_6, C_{2-6} alkynyl substituted with 0-2 R_6, C_{2-6} alkoxy substituted with 0-2 R_6, -NH(C_{2-6} alkyl) substituted with 0-2 R_6, -N(C_{2-6} alkyl)(C_{2-6} alkyl) where each C_{2-6} alkyl is independently substituted with 0-2 R_6, -XR_7, and Y;

R_6, R_7, R_8, X, Y, and Y′ are as defined for Formula IB.

Preferred compounds and salts of Formula VII include those wherein A is selected from NH, -CH=CH-, and CH_2NH; and R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, -NH(C_{1-4} alkyl), and -N(C_{1-4} alkyl)(C_{1-4} alkyl).

The invention includes compounds of Formula VIII



Formula VIII

and the pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and CH_2NH (NH is preferred);

R_4 is independently selected at each occurrence from hydrogen and C_{1-4}alkyl;

R_5 represents 0 to 2 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, and -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6;

R_9 represents 0 to 2 substituents and is independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, and -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is independently substituted with 0-2 R_6;

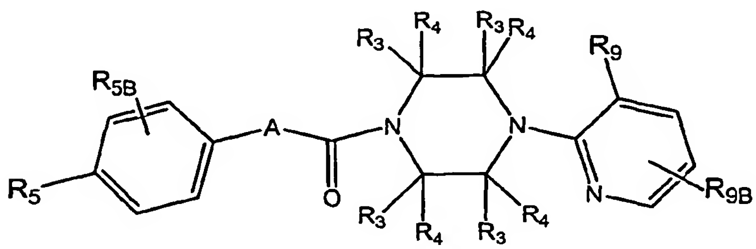
R_{5A} is independently selected from the group consisting of halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), and -N(C_{1-6} alkyl)(C_1-C_6 alkyl);

R_{9B} is independently selected from the group consisting of trifluoromethoxy, hydroxy, C_{2-6} alkyl, C_{2-6} alkoxy, -NH(C_{2-6} alkyl), and -N(C_{2-6} alkyl)(C_{2-6} alkyl); and

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, -NH(C_{1-4} alkyl), and -N(C_{1-4} alkyl)(C_{1-4} alkyl).

Preferred compound of Formula VIII are those wherein one of R_4 is hydrogen and the other is methyl.

A particularly preferred embodiment of the invention includes compounds of Formula IX



Formula IX

and the pharmaceutically acceptable salts thereof, wherein:

A, R_3, and R_4 are as defined for Formula I or for Formula IB;

R_5 is selected from the group consisting of bromo, fluoro, iodo, halo(C_{1-6})alkyl, halo(C_{3-6})alkoxy, C_{3-6}alkyl substituted with 0-3 R_6, C_{2-6}alkenyl substituted with 0-3 R_6, C_{2-6}alkynyl substituted with 0-3 R_6, C_{3-6}alkoxy substituted with 0-2 R_6, (C_{3-8}cycloalkyl)C_{1-4}alkyl, -NH(C_{1-6}alkyl) substituted with 0-2 R_6, -N(C_{1-6}alkyl)(C_{1-6}alkyl) where each C_{1-6}alkyl is substituted with 0-2 R_6, Y, -(C=O)Y, -(CH_2)Y, and -(CH(CN))Y;

R_9 is selected from the group consisting of halogen, cyano, -N(SO_2C_{1-6}alkyl)(SO_2C_{1-6}alkyl), -SO_2NH_2, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, C_{1-6}alkyl substituted with 0-2 R_6, C_{2-6}alkenyl substituted with 0-2 R_6, C_{2-6}alkynyl substituted with 0-2 R_6, C_{1-6}alkoxy substituted with 0-2 R_6, -NH(C_{1-6}alkyl) substituted with 0-2 R_6,

$-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each $C_{1-6}alkyl$ is substituted with 0-2 R_6;

R_{5B} and R_{9B} each represent from 0 to 2 substituents and are independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, $C_{1-6}alkyl$ substituted with 0-2 R_6, ($C_{3-8}cycloalkyl$)$C_{1-4}alkyl$ substituted with 0-2 R_6, $C_{2-6}alkenyl$ substituted with 0-2 R_6, $C_{2-6}alkynyl$ substituted with 0-2 R_6, $C_{1-6}alkoxy$ substituted with 0-2 R_6, $-NH(C_{1-6}alkyl)$ substituted with 0-2 R_6, and $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each $C_{1-6}alkyl$ is independently substituted with 0-2 R_6, and Y; and any two

R_5 and R_{5B} bound to adjacent atoms may be joined to form a $C_{3-8}cycloalkyl$ group or a heterocycloalkyl group, each of which is optionally substituted by from 1 to 5 substituents independently chosen from cyano, halogen, hydroxy, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, halo($C_{1-4}$)alkyl, and halo($C_{1-4}$)alkoxy, wherein the heterocycloalkyl group consists of from 4 to 8 atoms and contains 1, 2, or 3 heteroatoms selected from N, O, and S; and

R_6, R_7, R_8, X, Y, and Y' are as defined for Formula IB.

Preferred compounds and salts of Formula IX are those wherein A is O or NR_A, wherein R_A is hydrogen or methyl.

More preferred compounds and salts of Formula IX are those wherein

A is O or NR_A, wherein R_A is hydrogen or methyl; and

R_3 and R_4 are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, $C_{1-6}alkyl$,

C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

Other preferred compounds and salts of Formula IX are those wherein:

A is O or NR_A, wherein R_A is hydrogen or methyl;

R_3 is hydrogen; and

R_4 is independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

Still more preferred compounds and salts of Formula IX are those wherein

A is O, NR_A, wherein R_A is hydrogen or methyl;

R_3 is hydrogen; and

R_4 is independently chosen at each occurrence from hydrogen and C_{1-6}alkyl.

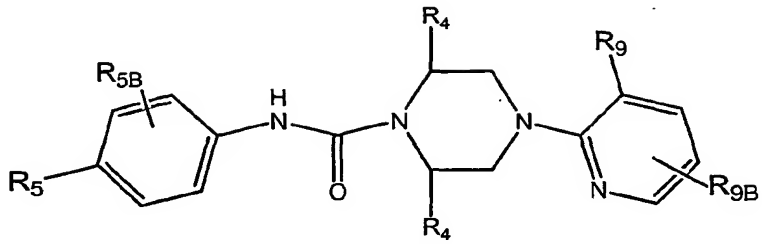
Another group of preferred compounds and salts of Formula IX is the group wherein

A is NR_A, wherein R_A is hydrogen or methyl;

R_3 is hydrogen; and

R_4 is independently chosen at each occurrence from hydrogen, halo(C_{1-3})alkyl, and C_{1-6}alkyl, but more preferably R_4 is chosen from hydrogen and C_{1-4} alkyl.

A particular class of compounds of Formula IX is represented by Formula IX-A

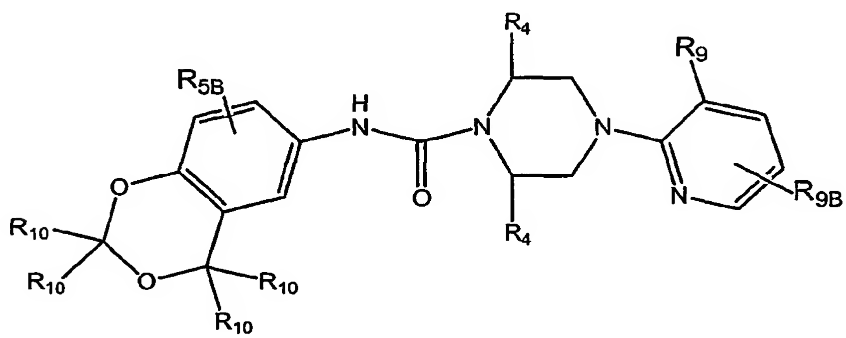


and the pharmaceutically acceptable salts thereof, wherein:

R_5, R_{5B}, R_9, and R_{9B} are as defined for Formula IX; and

R_4 is independently chosen at each occurrence from hydrogen and C_{1-4}alkyl.

Another class of compounds of Formula IX is represented by Formula IX-B:



Formula IX-B

and the pharmaceutically acceptably salts thereof, wherein:

R_{5B} and R_{9B} are independently chosen from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{10} is independently chosen at each occurrence from hydrogen, halogen, and C_{1-4} alkyl.

Preferred compounds and salts of Formula IX-B are those wherein R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo(C_{1-3})alkyl, C_{1-3}alkoxy, $-NH(C_{1-3}$alkyl), and $-N(C_{1-3}$alkyl)(C_{1-3}alkyl).

Other preferred compounds and salts of Formula IX-A and Formula IX-B are those wherein R_{5B} and R_{9B} are independently chosen from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy.

Still other preferred compounds and salts of Formula IX-A and Formula IX-B are those wherein:

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, and C_{1-2}alkyl, and C_{1-2}alkoxy.

The invention is further directed to compounds and salts of Formula IX-A and IX-B, wherein:

R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo(C_{1-3})alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-3}alkyl)(C_{1-3}alkyl);

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, and C_{1-2}alkyl, and C_{1-2}alkoxy.

For Formula IX-A, preferred substituents are

R_5 is selected from the group consisting of bromo, fluoro, iodo, halo(C_{1-6})alkyl, halo(C_{3-6})alkoxy, C_{3-6}alkyl substituted with 0-3 R_6, C_{2-6}alkenyl substituted with 0-3 R_6, Y, -(C=O)Y, -(CH_2)Y, and -(CH(CN))Y;

R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, halo(C_{1-2})alkyl, C_{1-3}alkoxy, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl);

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, amino, C_{1-4}alkyl, and C_{1-2}alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C_{1-2})alkyl, and C_{1-2}alkyl, and C_{1-2}alkoxy.

Particularly preferred definitions of R_6 for compounds and salts of this class are cyano, halogen, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -NH(C_{1-4}alkyl), and -N(C_{1-4}alkyl)(C_{1-4}alkyl) and Y; where

Y is independently selected at each occurrence from C_{3-8} cycloalkyl, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, and imidazolyl, each of which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4}alkylthio.

Particularly preferred definitions of R_9 and R_{9B} for compounds of Formula IX-A are:

R_9 is cyano, trifluoromethyl, chloro, or iodo; and

R_{9B} is hydrogen.

Particularly preferred definitions of R_5 for compounds of Formula IX-A are isopropyl, t-butyl, 2-butyl, trifluoromethyl, cyclopentyl, cyclohexyl, and heptafluoropropyl.

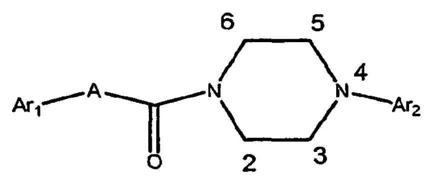
The invention is particularly directed to compounds and pharmaceutically acceptable salts of Formula IB, Formula II, Formula III, Formula IV, Formula V, Formula VII and Formula IX in which:

R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen and C_{1-6}alkyl; for the variables R_3, R_4, and R_5 haloalkyl is halo(C_{1-6})alkyl, i.e. a haloalkyl group having from 1 to 6 carbon atoms and from 1 to maximum allowable number of halogen substituents on those carbon atoms, haloalkoxy is halo(C_{1-6})alkoxy; alkyl is C_{1-6}alkyl, alkenyl is C_{2-6}alkenyl; alkynyl is C_{2-6}alkynyl; alkoxy is C_{1-6}alkoxy, -NH(alkyl) is -NH(C_{1-6}alkyl), and -N(alkyl)(alkyl) is -N(C_{1-6}alkyl)(C_{1-6}alkyl),

for the variables R_6, R_7, R_8, Y and Y' alkyl is C_{1-4}alkyl, alkoxy (or -O(alkyl) is C_{1-4}alkoxy (or -O(C_{1-4}alkyl)), -NHalkyl (or monoalkylamino) is -NH(C_{1-4}alkyl) (or mono(C_{1-4}alkyl)amino), -N(alkyl)(alkyl) (also dialkylamino) is -N(C_{1-4}alkyl)(C_{1-4}alkyl) (also di(C_{1-4}alkyl)amino), -S(O)$_n$alkyl is -S(O)$_n$(C_{1-4}alkyl), haloalkyl is halo(C_{1-4})alkyl, haloalkoxy is halo(C_{1-4})alkoxy, -CO(alkyl) is -CO(C_{1-4}alkyl), -CONH(alkyl) is -CONH(C_{1-4}alkyl), and -CON(alkyl)(alkyl) is -CON(C_{1-4}alkyl$_1$)(C_{1-4}alkyl$_2$); -NHC(O)(alkyl) is -NHC(O)(C_{1-4}alkyl), -N(alkyl)C(O)(alkyl) is -N(C_{1-4}alkyl)C(O)(alkyl), -NHS(O)$_n$(alkyl) is -NHS(O)$_n$(C_{1-4}alkyl), -S(O)$_n$NH(C_{1-4}alkyl), -S(O)$_n$N(alkyl)(alkyl) is -S(O)$_n$N(C_{1-4}alkyl)(C_{1-4}alkyl);

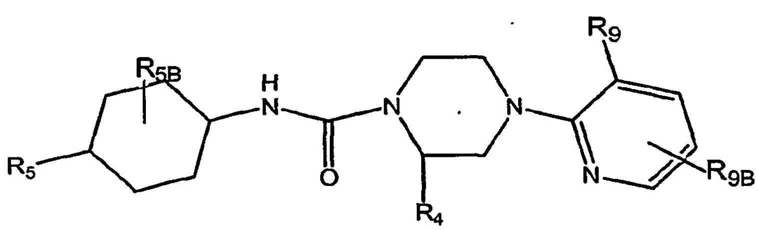
and alkylthio is C_{1-4}alkylthio.

Preferred compounds and salts of Formula V, Formula VI, Formula VII and Formula IX are those wherein R_3 and R_4 are independently selected at each occurrence from the group consisting of hydrogen and C_{1-6} alkyl. More preferred compounds and salts of Formula V are those wherein R_3 is hydrogen and the R_4 substituents present on the 3 and 5 positions of the piperazine ring are hydrogen and the R_4 substituents on the 2 and 6 position of the piperazine ring are independently hydrogen or C_{1-4} alkyl. For this discussion thhe piperazine ring is numbered as follows:

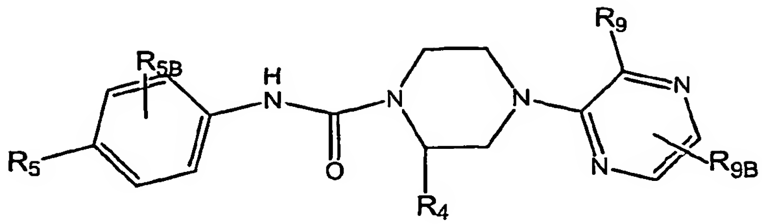


Even more preferred compounds and salts of Formula V are those wherein R_4 is methyl at the 2 position of the piperazine ring and R_3 and R_4 are hydrogen at all other positions.

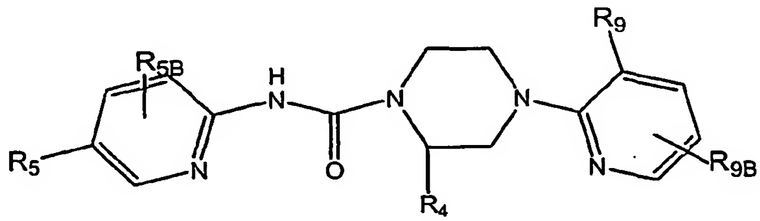
The invention particularly includes compounds Formula A-1, Formula B-1, Formula C-1, Formula D-1, Formula E-1, and Formula F-1



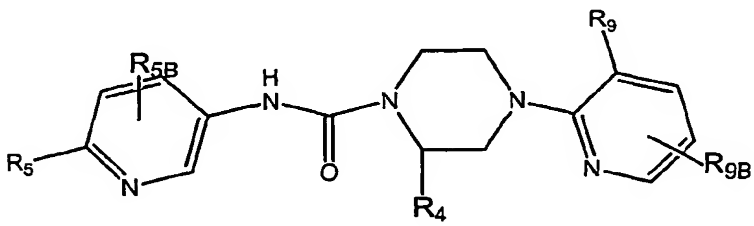
Formula A-1



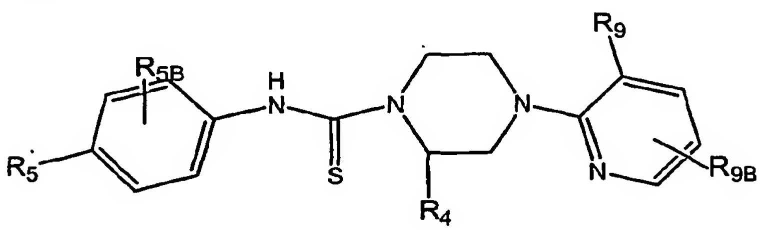
Formula B-1



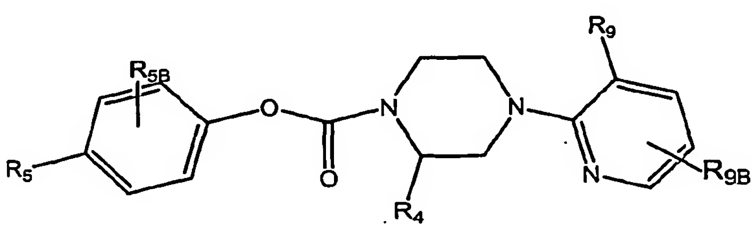
Formula C-1



Formula D-1



Formula E-1



Formula F-1

and the pharmaceutically acceptable salts of Formula A-1, Formula B-1, Formula C-1, Formula D-1, Formula E-1, and Formula F-1 wherein:

R_5 and R_9 are independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -NH(C_{1-6}alkyl, -N(C_{1-6}alkyl)(C_{1-6}alkyl), and C_{3-8} cycloalkyl; and

R_{5B} and R_{9B} each represent up to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3}alkyl, C_{1-3}alkoxy, -NH(C_{1-3}alkyl), and -N(C_{1-6}alkyl)(C_{1-6}alkyl).

Especially preferred compounds and salts of Formula A-1, Formula B-1, Formula C-1, Formula D-1, Formula E-1, and Formula F-1 are those wherein:

R_5 is C_{3-6} alkyl; C_{3-6} alkoxy; halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, or C_{3-8} cycloalkyl;

R_9 is chloro or trifluomethyl; and

R_{5B} and R_{9B} are hydrogen.

Representative compounds of the invention are shown in Table I below:

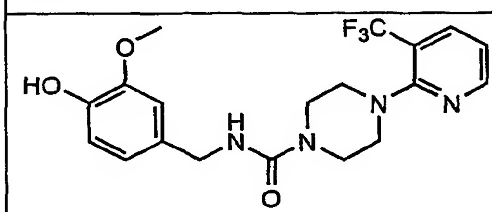
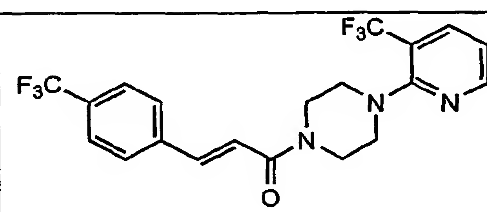
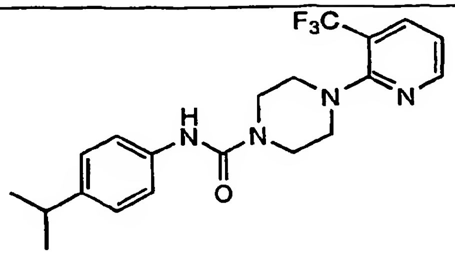
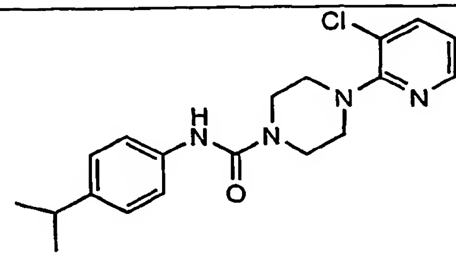
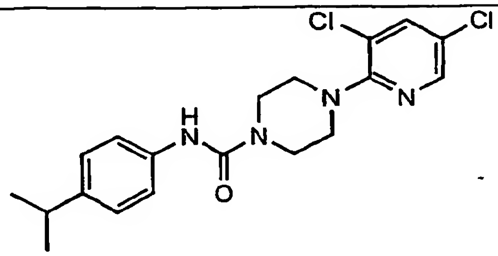
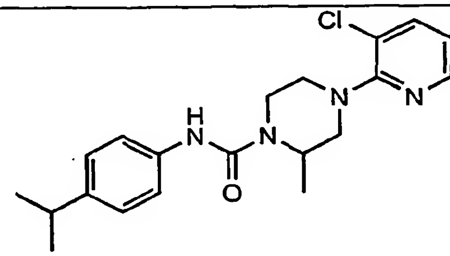
TABLE I	
 Compound 1	 Compound 2

TABLE I	
 Compound 3	 Compound 4
 Compound 5	 Compound 6

In one aspect invention relates to diaryl piperazines and related compounds that bind with high affinity to capsaicin receptors, including human capsaicin receptors. Compounds that bind with high affinity for the capsaicin receptor include compounds exhibit K_i values of less than 10 uM, and preferably exhibit K_i values of less than 1 uM, more preferably exhibit K_i values of less than 100 nM, and most preferably exhibit K_i values of less than 10 nM at the capsaicin receptors. This invention also includes diaryl piperazines that bind with high selectivity to capsaicin receptor. Compounds that exhibit high selectivity for the capsaicin receptor exhibit at least 20-fold, and preferably at least 100-fold greater affinity for the capsaicin receptor than for other cell surface receptors (e.g., NPY Y5 receptors, NPY Y1 receptors, $GABA_A$ receptors, MCH receptors, Bradykinin receptors, C5a receptors, androgen receptors, and the like).

Without wishing to be bound to any particular theory of operation, it is believed that the interaction of the compounds of Formulae I-IX and Formulae A-F with the capsaicin receptor results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a disorder responsive to capsaicin receptor modulation. Thus, as used herein, the term treatement encompases both disease modifying treatment and symptomatic treatment.

The diseases and/ or disorders that can also be treated using compounds and compositions according to the invention (which are examples of disorders responsive to capsaicin receptor modulation) include:

Chronic and acute pain conditions, including toothache, postherpetic neuralgia, diabetic neuropathy, postmastectomy pain syndrome, stump pain (and phantom limb pain), reflex sympathetic dystrophy, trigeminal neuralgia, oral neuropathic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, "burning-mouth" syndrome, and pain due to bilateral peripheral neuropathy. Preferred pain conditions for treatment in accordance with the invention are neuropathic pain conditions, including causalgia (reflex sympathetic dystrophy - RSD, secondary to injury of a peripheral nerve; this type of pain is generally considered to be non-responsive or only partially responsive to conventional opioid analgesic regimens), neuritis -including, e.g., sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, and neuronitis, and neuralgias -including those mentioned above and, e.g., cervicobrachial neuralgia,

cranial neuralgia, geniculate neuralgia, glossopharyngial neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia. Additional pain conditions that can be treated in accordance with the invention include headache - particularly those involving peripheral nerve activity including, e.g., sinus, cluster (i.e., migranous neuralgia, supra) and some tension and migraine headache conditions -, labor pains, Charcot's pains, gas pains, menstrual pain, root pain, homotopic pain and heterotopic pain - including cancer associated pain, pain (and inflammation) associated with venom exposure, e.g., due to snake bite, spider bite, or insect sting, and traumatic, e.g., post-surgical pain and burn pain. A preferred condition that can be treated in accordance with the invention is pain (as well as broncho-constriction and inflammation) due to exposure (e.g., via ingestion, inhalation, or eye contact) of mucous membranes to capsacin and related irritants such as tear gas, hot peppers, or pepper spray.

Itching conditions, including psoriatic pruritis, itch due to hemodyalisis, aguagenic pruritus, and itching associated with vulvar vestibulitis, contact dermatitis, insect bites and skin allergies.

Urinary incontenience, including detrusor hyperflexia of spinal origin and bladder hypersentivity.

The invention also provides pharmaceutical compositions comprising compounds of the invention, including packaged pharmaceutical compositions for treating disorders responsive to capsaicin receptor modulation. The packaged pharmaceutical

compositions include a container holding a therapeutically effective amount of at least one capsaicin receptor modulator as described supra and instructions (e.g., labeling) indicating the contained capsaicin receptor ligand is to be used for treating a disorder responsive to capsaicin receptor modulation in the patient.

The present invention also pertains to methods of inhibiting the binding of vanilloid (capsaicin analog) compounds, such as capsaicin, olvanil and RTX, to capsaicin receptors, which methods involve contacting a compound of the invention with cells expressing capsaicin receptors, wherein the compound is present at a concentration sufficient to inhibit vanilloid binding to capsaicin receptors *in vitro*. The methods of the invention include inhibiting the binding of vanilloid compounds to capsaicin receptors *in vivo*, e.g., in a patient given an amount of a compound of Formulae I-IX and Formulae A-F that results in and *in vivo* concentration in a body fluid sufficient to inhibit the binding of capsaicin compounds to capsaicin receptors *in vitro*. In one embodiment, such methods are useful in treating the effects of tear gas, hot pepper or pepper spray exposure. The amount of a compound that would be sufficient to inhibit the binding of a vanilloid compound to the capsaicin receptor may be readily determined via a capsaicin receptor binding assay, such as the assay described in Example 10 or by an assay of capsaicin receptor antagonism e.g, as in Example 11. The capsaicin receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of mammalian dorsal root ganglion (DRG) or from cells expressing cloned rat or human capsaicin receptors.

The present invention also pertains to methods for altering the signal-transducing activity, particularly the calcium ion conductance, mediated by capsaicin receptors, said method comprising exposing cells expressing such receptors to a solution comprising a compound of the, wherein the compound is present in the solution at a concentration sufficient to specifically alter the calcium conductance activity in response to capsaicin or RTX in vitro in cells expressing capsaicin receptors, preferred cells for this purpose are those that express high levels of capsaicin receptors (i.e., equal to or greater than the number of capsaicin receptors per cell found in rat DRG cells).. This method includes altering the signal-transducing activity of capsaicin receptors *in vivo*. Preferably such alterations are reductions of calcium flux. The amount of a compound that would be sufficient to alter the signal-transducing activity of capsaicin receptors may be determined in vitro via a capsaicin receptor signal transduction assay, such as the calcium mobilization (conductance, flux) assay described in Example 11. The amount of a compound that would be sufficient to alter the calcium conductance activity in response to capsaicin or RTX of capsaicin receptors may also be determined via an assay of capsaicin receptor mediated calcium conductance, such as an assay wherein the binding of capsaicin to a cell surface capsaicin receptor effects changes in the fluorescence of a calcium sensitive dye or in the expression of a calcium sensitive reporter gene.

The invention further provides:

A method of reducing the calcium conductance of a capsaicin receptor, which method comprises:

contacting a first solution comprising a fixed concentration of a capsaicin receptor agonist and a compound or

salt of the invention with a cell expressing the capsaicin receptor, wherein the compound or salt is present in the solution at a concentration sufficient to produce a detectable reduction of the calcium mobilization effects of the capsaicin receptor agonist when tested in an in vitro assay in which cells expressing a capsaicin receptor are contacted with a second solution comprising the fixed concentration of capsaicin receptor agonist and the compound or salt and the same method wherein: the cell expressing the capsaicin receptor is a neuronal cell that is contacted in vivo in an animal, and wherein the first solution is a body fluid of said animal; or the animal is a human patient.

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or salt of the invention; and a package comprising the pharmaceutical composition in a container and further comprising indicia comprising instructions for using the composition to either alleviate pain; or to treat a patient suffering from urinary incontinence or to alleviate symptoms of exposure to capsaicin or tear gas.

A compound or salt of the invention wherein, in an in vitro assay of capsaicin receptor antagonism, the compound or salt exhibits capsaicin receptor antagonist activity, but in an in vitro assay of capsaicin receptor agonism the compound does not exhibit detectable agonist activity.

A compound or salt of the invention wherein a dose of the compound or salt sufficient to provide analgesia in an animal model for determining pain relief does not produce sedation in an animal model assay of sedation.

A method of treating a mammal suffering from at least one symptom selected from the group consisting of symptoms of exposure to capsaicin, symptoms of burns or irritation due to

exposure to heat, symptoms of burns or irritation due to exposure to light, symptoms of burns or irritation due to exposure to tear gas, and symptoms of burns or irritation due to exposure to acid, the method comprising administering to the mammal a therapeutic dose of a compound that:

a) is a high potency capsaicin receptor antagonist in an *in vitro* assay of capsaicin receptor antagonism,

b) exhibits no detectable agonist activity in an *in vitro* assay of capsaicin receptor agonism,

c) is not a capsaicin analog, and

d) when administered to an animal in an animal model assay of sedation, at five times the minimum dosage needed to provide analgesia in an animal model for determining pain relief, does not cause sedation,

wherein the therapeutic dose contains an amount of the compound that is effective to reduce severity of at least one of the at least one symptom and preferably wherein the compound is a compound of the invention.

A method of treating a mammal suffering from neuropathic pain, the method comprising administering to the mammal a therapeutic dose of a compound that is a capsaicin receptor antagonist, and in certain embodiments, wherein the compound is a compound of the invention.

A method of treating a mammal suffering from peripheral-nerve-mediated pain, e.g., neuropathic pain, the method comprising administering to the mammal a therapeutic dose of a compound that is a capsaicin receptor antagonist, wherein the compound:

a) is a high potency capsaicin receptor antagonist in an *in vitro* assay of capsaicin receptor antagonism,

b) exhibits no detectable agonist activity in an *in vitro* assay of capsaicin receptor agonism,

c) is not a capsaicin analog, and

d) when administered to an animal in an animal model assay of sedation, at five times the minimum dosage needed to provide analgesia in an animal model for determining pain relief, does not cause sedation,

wherein the therapeutic dose contains an amount of the compound that is effective to reduce the peripheral-nerve-mediated pain, and preferably wherein the pain is neuropathic pain and the compound is a compound of the invention, and preferably wherein the pain is associated with a condition selected from the group consisting of postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, Charcot's pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, bilateral peripheral neuropathy, causalgia, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia, vidian neuralgia, sinus headache, tension headache, labor, childbirth, intestinal gas, menstruation, cancer, and trauma.

A compound of the invention, wherein the compound is not addictive.

The capsaicin receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents for determining the ability of a compound to bind to the capsaicin receptor and to act as an agonist, antagonist, inverse agonist, mixed agonist/antagonist or the like.

More particularly compounds of the invention may be used for demonstrating the presence of VR1 receptors or other capsaicin receptors in cell or tissue samples. This may be done by preparing a plurality of matched cell or tissue samples, at least one of which is prepared as an experimental sample and at least one of which is prepared as a control sample. The experimental sample is prepared by contacting (under conditions that permit binding of capsaicin or RTX to capsaicin receptors within cell and tissue samples) at least one of the matched cell or tissue samples that has not previously been contacted with any compound or salt of the invention with an experimental solution comprising the detectably-labeled preparation of the selected compound or salt at a first measured molar concentration. The control sample is prepared by in the same manner as the experimental sample and is incubated in a solution that contains the same ingredients as the experimental solution but that also contains an unlabelled preparation of the same compound or salt of the invention at a molar concentration that is greater than the first measured molar concentration.

The experimental and control samples are then washed (using the same wash conditions) to remove unbound detectably-labeled compound. The amount of detectably-labeled compound remaining bound to each sample is then measured and the amount

of detectably-labeled compound in the experimental and control samples is compared. A comparison that indicates the detection of a greater amount of detectable label in the at least one washed experimental sample than is detected in any of the at least one washed control samples demonstrates the presence of capsaicin receptors in that experimental sample.

The detectably-labeled compound used in this procedure may be labeled with any detectable label, such as a radioactive label, a biological tag such as biotin (which can be detected by binding to detectably-labeled avidin), an enzyme (e.g., alkaline phosphatase, beta galactosidase, or a like enzyme that can be detected its activity in a colorimetric, luminescent, or like assay) or a directly or indirectly luminescent label. When tissue sections are used in this procedure and the detectably-labeled compound is radiolabeled, the bound, labeled compound may be detected autoradiographically to generate an autoradiogram. When autoradiography is used, the amount of detectable label in an experimental or control sample may be measured by viewing the autoradiograms and comparing the exposure density of matched regions of the autoradiograms.

Labeled derivatives the capsaicin receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT) to characterize and localize capsaicin receptors in vivo.

Definitions

The compounds herein described may have one or more asymmetric centers or planes. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by

resolution of racemic forms (racemates), by asymmetric synthesis, or by synthesis from optically active starting materials. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral (enantiomeric and diastereomeric), and racemic forms, as well as all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound. The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers, By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^*, then said group may optionally be

substituted with up to two R^* groups and R^* at each occurrence is selected independently from the definition of R^*. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As indicated above, various substituents of the various formulae are "optionally substituted", including Ar_1, Ar_2, R_3 and R_4 of Formulae I-IX and Formulae A-F, and such substituents as recited in the sub-formulae such as Formula Ia and the like. When substituted, those substituents (e.g., C_{1-6} alkyl, n, Ar_1, Ar_2, R_1, R_2, R_3, and R_4) may be substituted by other than hydrogen at one or more available positions, typically 1 to 3 or 4 positions, by one or more groups, such as, halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; carbocyclic aryl

having 6 or more carbons, particularly phenyl (e.g. an Ar group being a substituted or unsubstituted biphenyl moiety); arylalkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group; arylalkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group; or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl.

As used herein, "alkyl" is intended to include both branched, straight-chain, and cyclic alkyl groups, having the specified number of carbon atoms that may contain one or more double or triple bonds. "Lower alkyl" denotes an alkyl group having from 1 to about 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. Preferred alkyl groups are C_1-C_6 alkyl groups. Especially preferred alkyl groups are methyl, ethyl, propyl, butyl, 3-pentyl.

As used herein, "alkoxy", "C_1-C_6 alkoxy", or "lower alkoxy" in the present invention is meant an alkyl group attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. "Lower alkoxy" denotes an alkyl group having from 1 to about 6 carbon atoms.

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w =1 to (2v+1). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, and pentachloroethyl.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7-to 13-membered bicyclic or tricyclic moeity, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "carbocyclic aryl" indicates aromatic groups containing only carbon. Such aromatic groups may be further substituted.

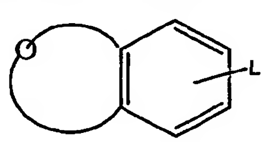
As used herein, the term "heterocyclic ring" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable

structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen atom in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "heteroaryl" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle. is not more than 1. The term "heterocycloalkyl" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic saturated ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S. Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl,

octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

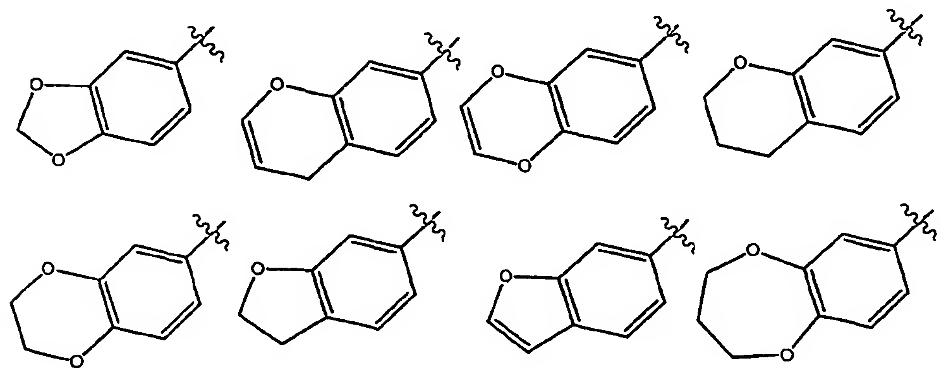
Preferred heterocycles include, but are not limited to, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl,. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "bicyclic oxygen-containing group" is meant to encompass a particular type of heteroaryl group of the formula:



where L indicates the point of attachment of the group to the structure of Formulae I-IX and Formulae A-F. The heterocyclic oxygen-containing ring has a total of from 5 to 7 members, and is saturated or unsaturated. Either ring of the bicyclic oxygen-containing group may be further substituted.

Examples of bicyclic oxygen-containing groups include any or all of the following structures:



Pharmaceutical preparations

Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutically acceptable prodrugs of the compounds encompassed by Formulae I-IX and Formulae A-F, which prodrugs are encompassed by the present invention. "Prodrugs" are intended to include any compounds that become compounds of Formulae I-IX and Formulae A-F when administered to a mammalian subject, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formulae I-IX and Formulae A-F. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide.

The compounds of general Formulae I-IX and general Formulae A-F may be administered orally, topically, parenterally, e.g., by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formulae I-IX and general Formulae A-F and a pharmaceutically acceptable carrier. One or more compounds of general Formulae I-IX and general Formulae A-F may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formulae I-IX and general Formulae A-F may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically

acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene

sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or

partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formulae I-IX and general Formulae A-F may also be administered in the form of suppositories, e.g., for rectal or vaginal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and

will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formulae I-IX and general Formulae A-F may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle where desirable.

Typical subjects to which compounds of the invention may be administered will be mammals, particularly primates, especially humans. For veterinary applications, a wide variety of subjects will be suitable, e.g. livestock such as cattle, sheep, goats, cows, swine and the like; poultry such as chickens, ducks, geese, turkeys, and the like; and other domesticated animals particularly pets (companion animals) such as dogs and cats. For diagnostic or research applications, a wide variety of mammals will be suitable subjects including rodents (e.g. mice, rats, hamsters), rabbits, primates, and swine such as inbred pigs and the like.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed or drinking water.

For systemic (as opposed to local or topical) administration, dosage levels of the order of from about 0.01 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of pain, urinary incontinence, or other

of the above-indicated conditions (about 0.05 mg to about 7 g per human patient per day). Preferred systemic doses for preferred high potency compounds of Formulae I-IX and Formulae A-F range from about 0.01 mg to about 50 mg per kilogram of body weight per subject per day, with oral doses generally being about 5-20 fold higher than intravenous doses. The most highly preferred compounds of the invention are orally active (e.g., provide a reduction of pain or a reduction of frequency of urinary incontinence) at doses ranging from 0.05 to 40 mg per kilogram of body weight per subject per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen (frequency of administration) of 4 times daily or less is preferred. For the treatment of chronic pain or urinary incontinence a dosage regimen of 2 times daily is more preferred and a frequency of administration of once a day is particularly preferred. For the treatment of acute pain a single dose that rapidly reaches effective concentrations is desirable.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of

excretion, drug combination and the nature and severity of the particular disease or condition undergoing treatment.

Preferred compounds of the invention will have certain desirable pharmacological properties. For systemic administration such properties include, but are not limited to high oral bioavailability, such that the preferred oral dosages and dosage forms discussed above can provide therapeutically effective levels of the compound *in vivo*, low serum protein binding and low first pass hepatic metabolism. For all types of administration low toxicity, and desirable *in vitro* and *in vivo* half-lifes are desired. While penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, low brain levels of compounds used to treat peripheral disorders (such as urinary incontinence, or chronic or acute pain that does not originate from the CNS) are often preferred.

Laboratory assays may be used to predict these desirable pharmacological properties. The discussion that follows is supplemented by the detailed protocols of Example 16, infra. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocyctes may be used to predict compound toxicity, with non-toxic compounds being preferred. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound, e.g., intravenously.

Percentage of serum protein binding may be predicted from albumin binding assays. Examples of such assays are described in a review by Oravcová, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27). Preferred compounds exhibit reversible serum protein binding. Preferably this binding is

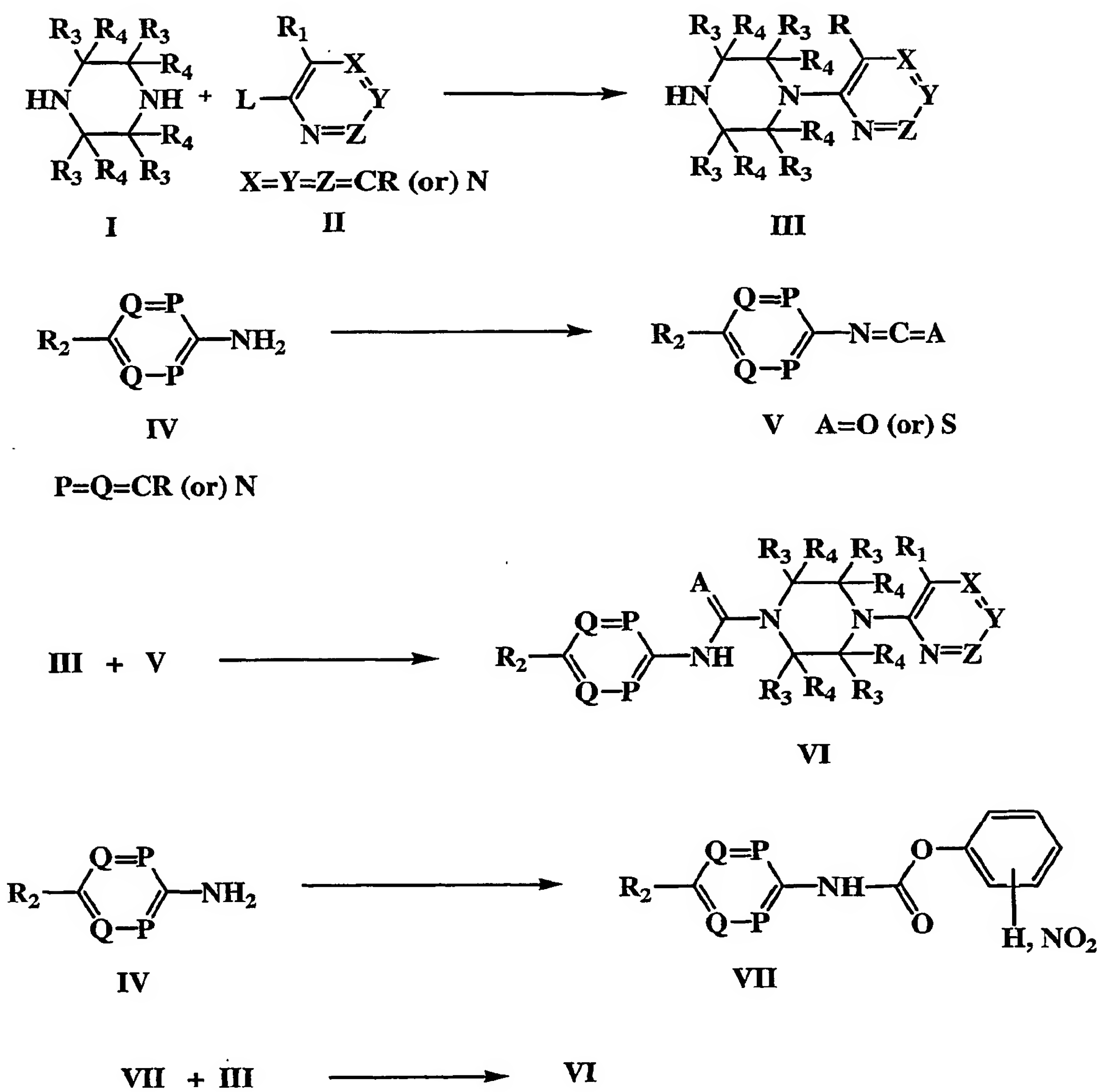
less than 99%, more preferably less than 95%, even more preferably less than 90%, and most preferably less than 80%.

Frequency of administration is generally inversely proportional to the *in vivo* half-life of a compound. *In vivo* half-lives of compounds may be predicted from the results of assays, e.g., *in vitro* assays of microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition*, 1998, volume 26, pages 1120-1127). Preferred half-lives are those allowing for a preferred frequency of administration.

Preparation of compounds

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Compounds of the present invention i.e. urea or thiourea derivatives (VI) can be synthesized by following the steps outlined in Scheme 1.

Scheme 1

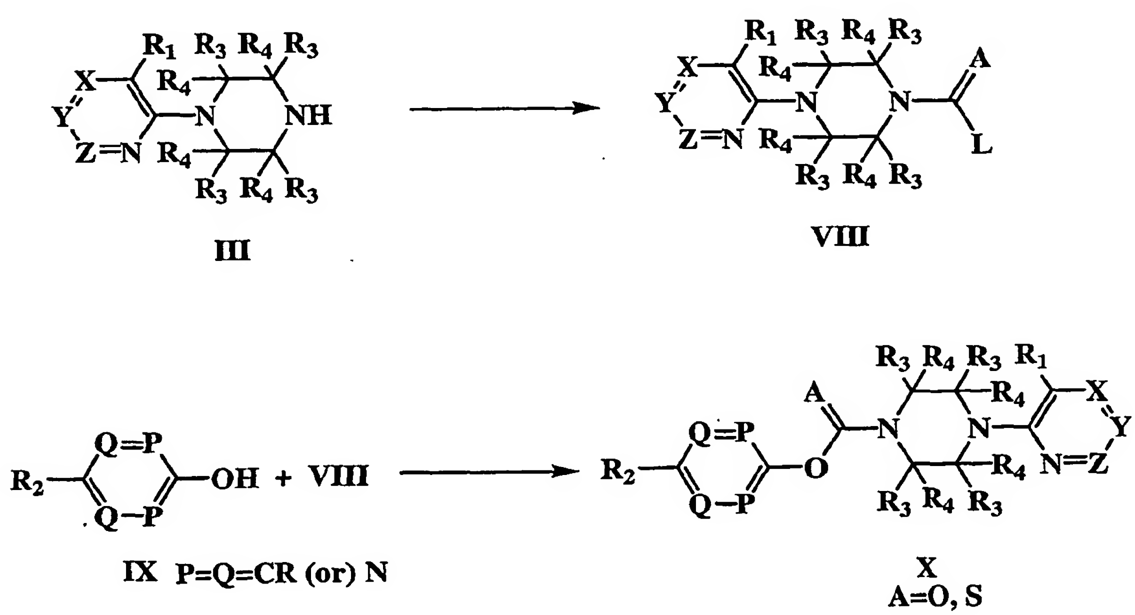


Intermediate III can be obtained by treating I with II in the presence of a base (eg: K_2CO_3, Cs_2CO_3, $NR_1R_2R_3$, NaOR, KOR) in an inert solvent such as N,N-dialkylformamide, N,N-dialkylacetamide, dialkylethers, cyclic ethers, DMSO, N-methyl-2-pyrrolidinone at temperatures ranging from -78 ^{o}C to 200 ^{o}C. Isocyanates or isothiocyanates of V can be obtained by treating

compound of IV with phosgene, thiophosgene, carbonyldiimidazole in an inert solvent such as benzene, toluene at temperatures ranging from -78 ^{0}C to 200 ^{0}C. The compound of present invention VI can be obtained by treating intermediates III with V in an organic solvent at temperatures -78 ^{0}C to 200 ^{0}C. Alternatively compound of VI can be prepared by treatment of intermediate VII with III in the presence of base such as triethylamine in an inert solvent such as chloroform at temperatures ranging from -78 ^{0}C to 200 ^{0}C.

Carbamates or thiocarbamates (X) of the present invention can be synthesized by following the steps outlined in Scheme 2.

Scheme 2



Intermediate III can be converted to VIII (A=O, S, L=halogen, imidazole) upon treatment with phosgene, thiophosgene or carbonyldiimidazoles. Compound of product X can be obtained by treatment with phenols (IX) with compound VIII

in the presence of a base in an inert solvent at temperatures ranging from -78 ^{0}C to 200 ^{0}C.

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present inventions, as demonstrated by the following examples. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

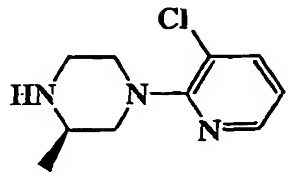
The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present inventions, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, such need for protecting groups, as well as the conditions necessary to attach and remove such groups, will be apparent to those skilled in the art of organic synthesis.

<u>EXAMPLES</u>

<u>EXAMPLE 1</u>

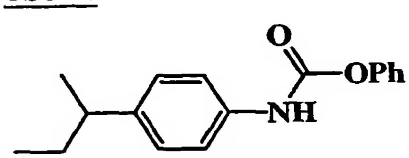
<u>(R)-4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazine-1-carboxylic acid (4-sec-butyl-phenyl)-amide</u>

<u>Part A: Synthesis of (R)-1-(3-Chloro-pyridin-2-yl)-3-methyl-piperazine</u>:



Dissolve 2,3-dichloropyridine (8.5 g, 0.057 moles) and (R)-(-)-2-methylpiperazine (5.75 g, 0.057 moles) in N,N-dimethylacetamide (125.0 mL) under nitrogen atmosphere. Add anhydrous powdered K_2CO_3 (23.75 g, 0.172 moles) to this mixture and stir at 135-140 °C for 48 h. New spot noticed in TLC (5 % MeOH / $CHCl_3$ / 1 % NEt_3) along with absence of starting materials. Cool the reaction mixture to room temperature, dilute with water (400 mL), extract with EtOAc (3 x 200 mL) and wash the combined organic extract with brine (2 x 150 mL). Dry over $MgSO_4$, concentrate under vacuum to afford crude product (20.0 g) as orange yellow liquid. Distil the crude under high vacuum to afford pyridylpiperazine derivative as yellow viscous oil (10 g, bp 112-115 °C /0.1 torr). NMR ($CDCl_3$): δ ..1.1-1.12 (d, 3H, J=1.6 Hz), 2.50-2.53 (t, 1H), 2.83-2.87 (m, 1H), 3.06-3.08 (m, 3H), 3.67-3.75 (m, 2H), 6.80-6.82(dd, 1H), 7.56-7.58 (dd, 1H), 8.17-8.18 (dd, 1H).

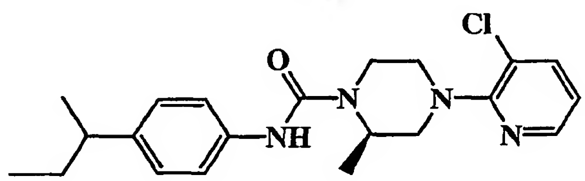
Part B: Synthesis of (4-sec-Butyl-phenyl)-carbamic acid phenyl ester:



Dissolve 4-isobutylaniline (4.5 g, 0.03 moles) in pyridine (30 mL) under nitrogen at room temperature. Add drop wise phenyl

chloroformate (3.75 mL, 0.03 moles) to the reaction mixture at room temperature. Stir the mixture for 3 days and new spot noticed in TLC (30 % EtOAc / hexane). Evaporate the reaction mixture under vacuo, partition between EtOAc and water (200 mL), wash several times with brine, dry ($MgSO_4$) and concentrate *in vacuo*. Purify the crude by flash column chromatography on a silica gel using (10 % EtOAc / hexanes) to afford white solid.

Part C: Title Compound:

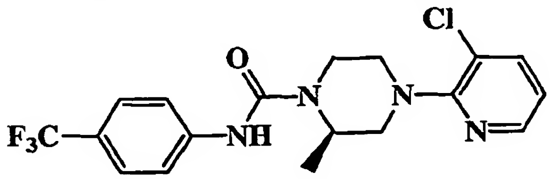


Dissolve Part A material of Example 1 (212 mg, 1.0 mmole) with Part B material of Example 1 (269 mg, 1.0 mmole) in $CHCl_3$ (10 mL) under nitrogen at room temperature. Add triethylamine (202 mg, 2.0 mmol) to the mixture and reflux for 4 hours. Cool the reaction mixture to room temperature, wash with 2N aq. NaOH, water and dry ($MgSO_4$). Evaporate the dried extract in vacuo and purify by flash column chromatography on a silica gel using $CHCl_3$ to afford white solid.

NMR ($CDCl_3$): δ 0.78-0.83 (t, 3H), 1.19-1.22 (d, 3H, J=2.2 Hz), 1.43-1.45 (d, 3H, J=2.3 Hz), 1.51-1.61 (m, 2H), 2.51-2.58 (m, 1H), 2.92-3.05 (m, 2H), 3.41-3.50 (m, 1H), 3.73-3.94 (m, 3H), 4.35 (m, 1H), 6.33 (bs, 1H), 6.86-6.90 (dd, 1H), 7.09-7.13 (m, 2H), 7.26-7.30 (m, 2H), 7.60-7.63 (dd, 1H), 8.18-8.20 (dd, 1H).

Example 2

(R)-(-)-4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazine-1-carboxylic acid (4-trifluoromethyl-phenyl)-amide



Dissolve Part A material of example 1 (0.2756 g, 1.3 mmoles) in toluene (1.5 mL) under nitrogen at room temperature. Add drop wise 4-trifluoromethylphenyl isocyanate (0.2431 g, 1.3 mmoles) dissolved in toluene (50 mL) to the mixture over a period of 30 mins and stir at room temperature for 3 hours. Evaporate the solvent from reaction mixture under vacuum to afford colorless oil. Crystallize the oil from 1:1 Et_2O / hexane (2.0 mL) to afford white solid.

NMR ($CDCl_3$): δ 1.45-1.47 (d, 3H, J=1.7 Hz), 2.97-3.01 (t, 1H), 3.06-3.10 (m, 1H), 3.47-3.50 (m, 1H), 3.75-3.85 (m, 2H), 3.92-3.95 (m, 1H), 4.37-4.38 (m, 1H), 6.59 (bs, 1H), 6.88-6.91 (dd, 1H), 7.52-7.56 (m, 4H), 7.61-7.63 (dd, 1H), 8.19-8.21 (dd, 1H).

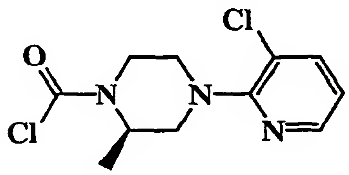
Mass spectrum (ESI): 399.3 (M+H).

Analysis calcd. for $C_{18}H_{18}ClF_3N_4O$: C, 54.21; H, 4.55; Cl, 8.89; F, 14.29; N, 14.05. Found: C, 54.47; H, 4.36; Cl, 8.50; F, 14.99; N, 13.94

Example 3

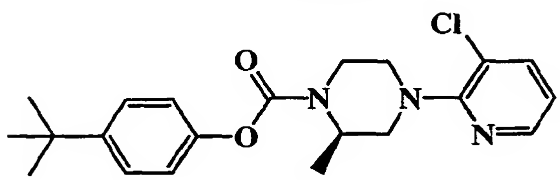
(R)-3-Chloro-pyridin-2-yl)-2-methyl-piperazine-1-carboxylic acid 4-tert-butyl-phenyl ester

Part A: Synthesis of (R)-4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazine-1-carbonyl chloride:



Dissolve Part A material of Example 1 (1.06 g, 5.0 mmole)) in CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (50 mL) under nitrogen at room temperature. Add drop wise 20 % $COCl_2$ in toluene (5.0 mL) at room temperature and stir overnight. Separate the organic layer, extract the aq. layer with CH_2Cl_2 (2 x 15 mL) and dry ($MgSO_4$). Evaporate the organic layer under vacuo to afford yellow oil.

Part B: Title Compound:



Dissolve Part A material of Example 3 (136 g, 0.5 mmole)) in pyridine (2.0 mL) under nitrogen at room temperature. Add 4-tert. butylphenol to the reaction mixture at room temperature and stir overnight. Evaporate the reaction mixture under vacuo, partition between water / CH_2Cl_2 (20 mL) and dry ($MgSO_4$). Evaporate the organic layer under vacuo and purify by flash column chromatography on silica gel using 15 % EtOAc / hexane to afford colorless oil.

NMR ($CDCl_3$): δ 1.28-1.31 (3 S, 9H), 1.35-1.48 (m, 3H), 2.96-3.11 (m, 2H), 3.49 (m, 1H), 3.72-3.80 (m, 2H), 4.13-4.24 (m,

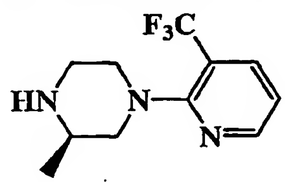
1H), 4.55-4.60 (m, 1H), 6.74-6.92 (m, 2H), 7.04-7.07 (m, 1H), 7.23-7.26 (m, 1H), 7.36-7.38 (m, 1H), 7.61-7.64 (m, 1H), 8.19-8.22 (m, 1H).

Mass spectrum (ESI): 388.2 (M+H).

Example 4

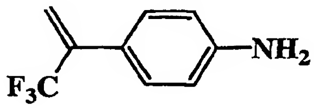
2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid [4-(2,2,2-trifluoro-1-methyl-ethyl)-phenyl]-amide

Part A : Synthesis of 3-Methyl-1-(3-trifluoromethyl-pyridin-2-yl)-piperazine



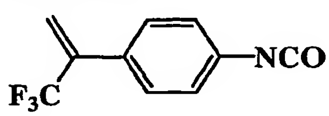
Dissolve 2-chloro-3-trifluoromethylpyridine (5.4 g, 0.03 moles) and (R)-(-)-2-methylpiperazine (3.0 g, 0.03 moles) in N,N-dimethylacetamide (100.0 mL) under nitrogen atmosphere. Add anhydrous powdered K_2CO_3 (12.4 g, 0.09 moles) to this mixture and stir at 135-140 °C for 24 h. New spot noticed in TLC (5 % MeOH / $CHCl_3$ / 1 % NEt_3) along with absence of starting materials. Cool the reaction mixture to room temperature, dilute with water (300 mL), extract with EtOAc (3 x 200 mL) and wash the combined organic extract with brine (2 x 150 mL). Dry over $MgSO_4$, concentrate under vacuum to afford crude product as orange yellow liquid. Purify by flash column chromatography using 1 % MeOH / $CHCl_3$ to afford yellow viscous oil.

Part B: Synthesis of 4-(1-Trifluoromethyl-vinyl)-phenylamine



Dissolve 4-(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)aniline (2.19 g, 0.01 moles) and 2-Bromo-3,3,3-trifluoro-propene (2.61 g, 0.015 moles) in 1:1 THF/1,2-dimethoxyethane (30 mL) and cooled in an ice bath under nitrogen atmosphere. Add $PdCl_2[(PPh_3)_2]$ (210 mg, 3 mol %) and $AsPh_3$ (459 mg, 15 mol %) to the reaction mixture followed by dropwise addition of 2.0 N Aq. NaOH (20 mL). Stirred the resultant mixture at room temp for 1 h followed by 70 ^{0}C for 15 h. Add additional 1.5 eq. of 2-Bromo-3,3,3-trifluoro-propene (2.61 g) to the reaction mixture and continued at 70 ^{0}C for 6 h. Evaporate the reaction mixture under vacuo, dissolve the residue in water/EtOAc (100 mL each), separate the organic layer, extract the aq. layer with EtOAc (2 x 100 mL), combine the organic layers and dry with MgSO4. Filter the dried extract, evaporate under vacuo and purify the crude by flash column chromatography on a silica gel using $CHCl_3$ to afford yellow oil.

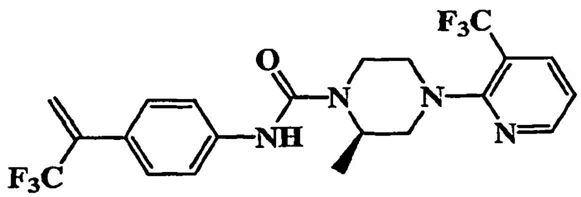
Part C: Synthesis of 1-Isocyanato-4-(1-trifluoromethyl-vinyl)-benzene



Cool 20 % phosgene in toluene (5.0 mL) to -40 ^{0}C under N2 atmosphere. Dissolve Part B material of Example 4 (0.47 g, 2.5 mmoles) in toluene and add dropwise to the cooled stirred

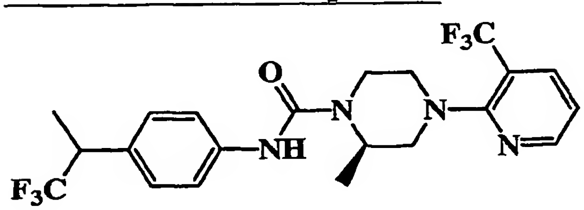
solution. Stir at -40 °C for 30 mins followed by room temperature for 1 h and then at reflux for 1 h. Concentrate in vacuo to afford orange yellow liquid.

Part D: Synthesis of 2-Methyl-4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid [4-(1-trifluoromethyl-vinyl)-phenyl]-amide



Dissolve Part A material of example 4 (0.123 g, 0.5 mmoles) in toluene (1.0 mL) under nitrogen at room temperature. Add drop wise Part C material of Example 4 (0.106 g, 0.5 mmoles) dissolved in toluene (1.0 mL) to the mixture over a period of 5 mins and stir at room temperature for 20 hours. Evaporate the solvent from reaction mixture under vacuum and purify by flash column chromatography using $CHCl_3$ to afford yellow oil.

Part E: Title compound:



Dissolve Part D material of example 4 (0.120 g, 0.262 mmoles) in EtOH(25.0 mL) at room temperature. Add 5 % Pd/C (30 mg) and hydrogenate at 5 atm. of H_2 for 5 hours at room temperature. Filter the catalyst, evaporate the solvent from reaction

mixture under vacuum and purify by PTLC using 5 % MeOH / $CHCl_3$ to afford yellow oil.

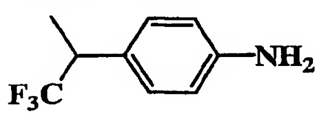
NMR ($CDCl_3$): δ 1.38-1.41 (d, 3H), 1.45-1.47 (d, 3H), 3.05-3.11 (m, 1H), 3.22-3.62 (m, 4H), 3.85-3.90 (m, 1H), 4.35-4.42 (m, 1H), 6.40 (s, 1H), 7.05-7.10 (m, 1H), 7.21-7.40 (m, 5H), 7.95-7.97 (d, 1H), 8.42-8.46 (d, 1H).

Mass spectrum (ESI): 461.3 (M+H).

Example 5

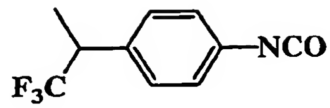
4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazine-1-carboxylic acid [4-(2,2,2-trifluoro-1-methyl-ethyl)-phenyl]-amide

Part A: Synthesis of 4-(2,2,2-Trifluoro-1-methyl-ethyl)-phenylamine



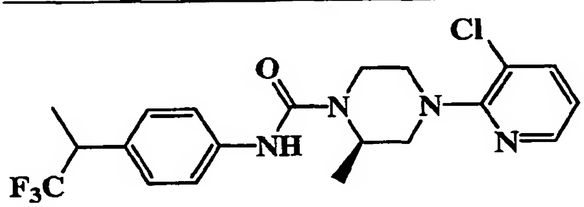
Dissolve Part B material of example 4 (0.375 g, 0.262 mmoles) in MeOH(25.0 mL) at room temperature. Add raney Ni (500 mg) and hydrogenate at 40 atm. of H_2 for 20 hours at room temperature. Filter the catalyst, evaporate the solvent from reaction mixture under vacuum and purify by flash column chromatography using $CHCl_3$ to afford yellow oil.

Part B: Synthesis of 1-Isocyanato-4-(2,2,2-trifluoro-1-methyl-ethyl)-benzene



Cool 20 % phosgene in toluene (2.0 mL) to -40 °C under N2 atmosphere. Dissolve Part A material of Example 5 (0.189 g, 1.0 mmole) in toluene and add drop wise to the cooled stirred solution. Stir at -40 °C for 30 mins followed by room temperature for 3 h and then at reflux for 18 h. Concentrate in vacuo to afford yellow liquid.

<u>Part C: Title compound:</u>



Dissolve Part A material of example 1 (0.169 g, 0.795 mmoles) in toluene (1.0 mL) under nitrogen at room temperature. Add drop wise Part B material of Example 5 (0.171 g, 0.795 mmoles) dissolved in toluene (1.0 mL) to the mixture over a period of 5 mins and stir at room temperature for 20 hours. Evaporate the solvent from reaction mixture under vacuum and purify by PTLC using 5 % MeOH / $CHCl_3$ to afford white amorphous powder.

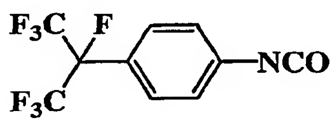
NMR ($CDCl_3$): δ 1.44-1.49 (2d, 6H), 2.94-3.11 (m, 2H), 3.36-3.51(m, 2H), 3.74-3.94 (m, 3H), 4.35-4.37 (m, 1H), 6.41 (s, 1H), 6.87-6.90 (dd, 1H), 7.23-7.26 (m, 2H), 7.36-7.38 (m, 2H), 7.60-7.63 (dd, 1H), 8.19-8.20 (dd, 1H).

Mass spectrum (ESI): 427.3 (M+H).

Example 6

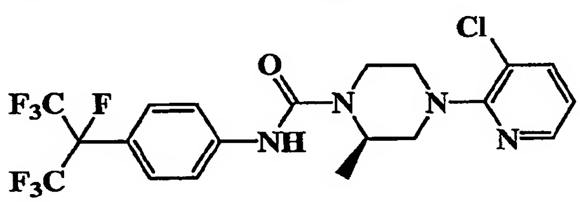
(R)-4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazine-1-carboxylic acid [4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-phenyl]-amide

Part A: Synthesis of 1-Isocyanato-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-benzene



Cool 20 % phosgene in toluene (20.0 mL) to -40 °C under N2 atmosphere. Dissolve 4-heptafluoroisopropylaniline (2.0 g, 7.7 mmoles; see: EP 1006102 for aniline preparation) in toluene (5.0 mL) and add drop wise to the cooled stirred solution. Stir at -40 °C for 30 mins followed by room temperature for 2 h and then at reflux for 4 h. Concentrate in vacuo to afford yellow liquid.

Part B: Title compound:



Dissolve Part A material of example 1 (0.106 g, 0.795 mmoles) in toluene (1.0 mL) under nitrogen at room temperature. Add drop wise Part A material of Example 6 (0.144 g, 0.5 mmoles) dissolved in toluene (1.0 mL) to the mixture over a period of 5 mins and stir at room temperature for 20 hours. Evaporate the

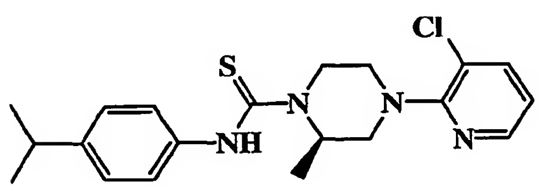
solvent from reaction mixture under vacuum and purify by PTLC using 5 % MeOH / $CHCl_3$ to afford white amorphous powder.

NMR ($CDCl_3$): δ 1.44-1.46 (d, 3H, J=1.6 Hz), 2.93-3.10 (m, 2H), 3.45-3.52 (m, 1H), 3.74-3.78 (m, 2H), 3.91-3.94 (m, 1H), 4.37-4.38 (m, 1H), 6.60 (s, 1H), 6.87-6.90 (dd, 1H), 7.52-7.60 (m, 4H), 7.61-7.63 (m, 1H), 8.18-8.20 (dd, 1H).

Mass spectrum (ESI): 499.2 (M+H).

Example 7

4-(3-Chloro-pyridin-2-yl)-2-methyl-piperazine-1-carbothioic acid (4-isopropyl-phenyl)-amide



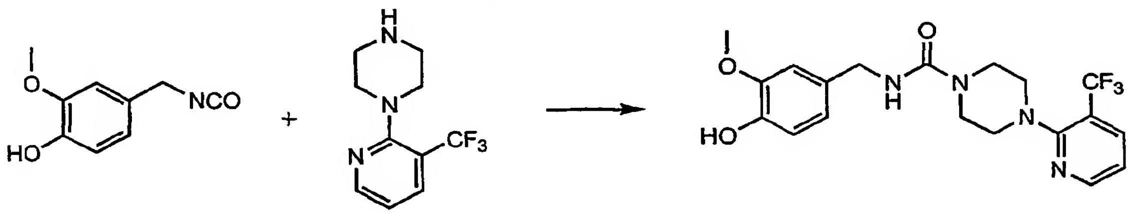
Dissolve Part A material of example 1 (0.212 g, 1.0 mmoles) in toluene (1.0 mL) under nitrogen at room temperature. Add drop wise 4-isopropylisothiocyanate (0.177 g, 0.5 mmoles) dissolved in toluene (1.0 mL) to the mixture over a period of 5 mins and stir at room temperature for 20 hours. Evaporate the solvent from reaction mixture under vacuum and purify by flash column chromatography using $CHCl_3$ to afford white solid (mp 49-51 ^{0}C).

NMR ($CDCl_3$): δ 1.22-1.25 (d, 3H), 1.41-1.43 (d, 3H), 2.80-3.20 (m, 3H), 3.45-3.60 (m, 1H), 3.65-3.80 (m, 2H), 4.35-4.39 (m, 1H), 5.05-5.20 (m, 1H), 6.85-6.90 (s, 1H), 7.15-7.35 (m, 5H), 7.42-7.44 (d, 1H), 8.18-8.20 (d, 1H).

Mass spectrum (ESI): 387.2 (M+H).

Example 8

Synthesis of 4-(3-Trifluoromethyl-2-pyridinyl)-N-(3-methoxy-4-hydroxyphenylmethyl)-1-piperazinecarboxamide



A quantity of 0.2 mL of a 0.2 M isocyante solution in dichloroethane is treated with 0.26 mL of a 0.2 mL solution of piperazine in 95:5 toluene: N-Methyl Morphine at 60 °C for 16 hr. The resulting reaction solution was cooled to room temperature. To the resulting solution is added 1 drop of amino propyl morpholine and warmed to 60 °C for an additional hour. The resulting mixture is cooled to room temperature and chromatographed SiO_2 with ethyl acetate to afford 10 mg 63% of the title compound (Compound 1). MS m/z 410.16 found: 411, 433 Na adduct. Capsaicin rececptor K_i: 366nM

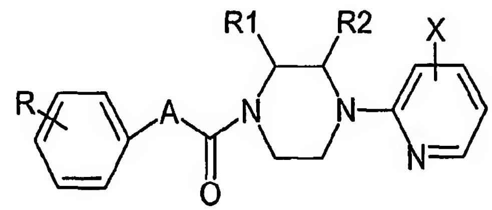
Example 9

Additional compounds

Using variations of the methods given in Schemes 1 and 2, and Examples 1-8 that will be readily apparent to one skilled in the art of organic synthesis the compounds list in Tables II, III and IV are prepared. Commercial grade reagents are

used without further purification in the preparation of these compound

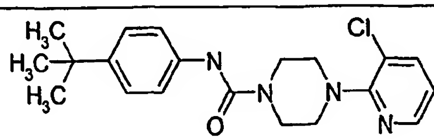
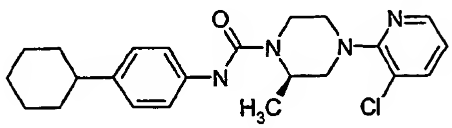
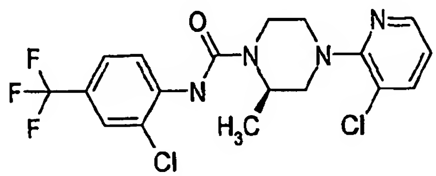
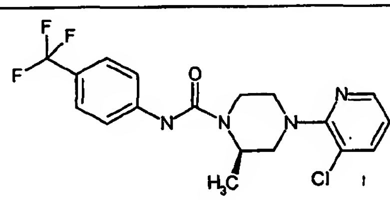
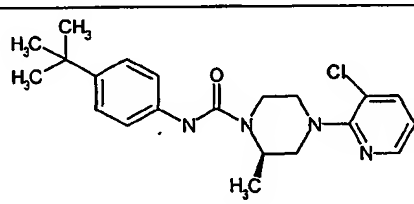
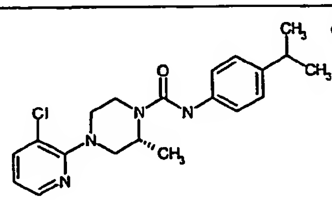
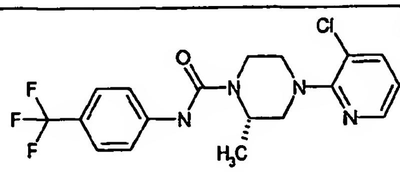
TABLE II

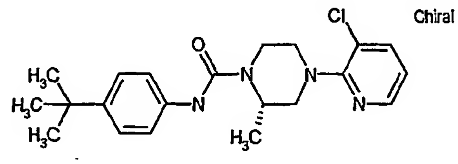
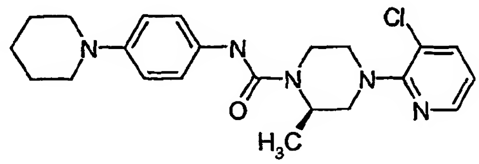
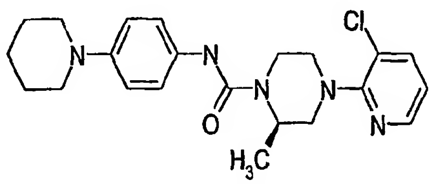
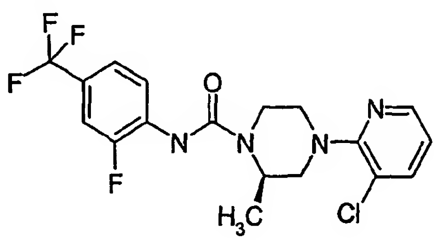
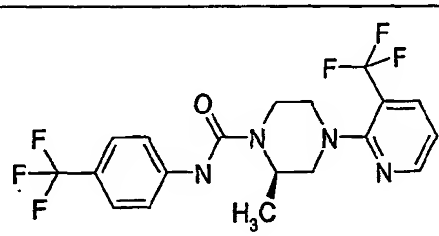
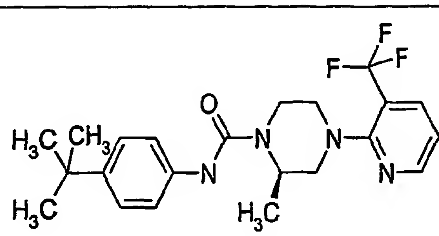


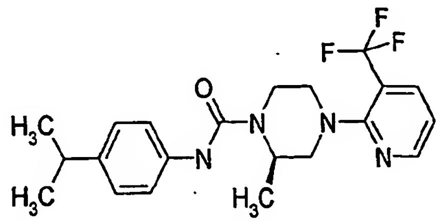
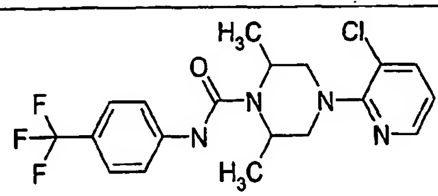
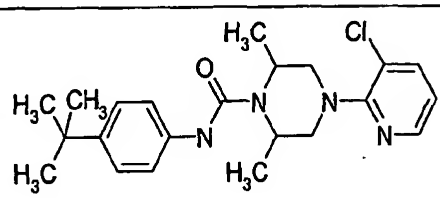
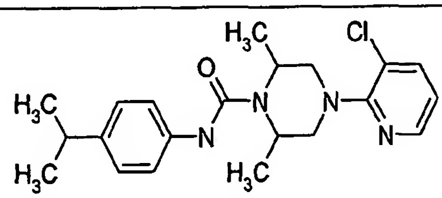
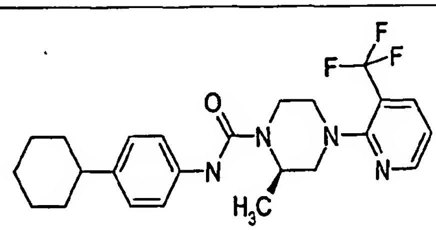
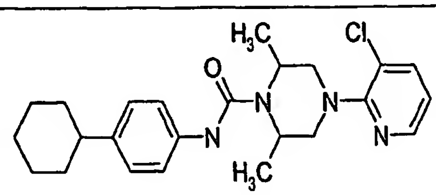
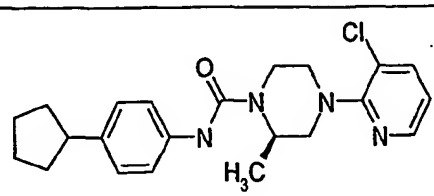
Compound	R	R1	R2	A	X	Calc	Found	Activity	Chemical Name
2	4-Butyl	H	H	NH	3-NO2	383	384, 406 Na adduct	*	4-(3-Nitro-2-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide
3	4-Butyl	H	H	NH	3-CF3	406	407, 429 Na adduct	*	4-(3-Trifluoromethyl-2-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide
4	4-Isopropyl	H	H	NH	3-Me	338	339, 361 Na adduct	*	4-(3-Methyl-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-Piperazinecarboxamide
5	4-Butyl	H	H	NH	3-Me	352	353, 375 Na adduct	NA	4-(3-Methyl-2-pyridinyl)-N-[4-(n-butyl)phenyl]-1-piperazinecarboxamide
6	4-Isopropyl	H	H	NH	3-CF3	352	353, 375 Na adduct	*	4-(3-Trifluoromethyl-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide
7	4-Isopropyl	H	H	NH	3-Cl,5-CF3	427	427, 449 Na adduct	*	4-(3-Chloro-5-trifluoromethyl-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide

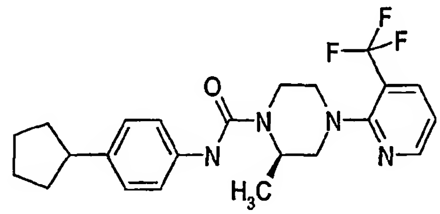
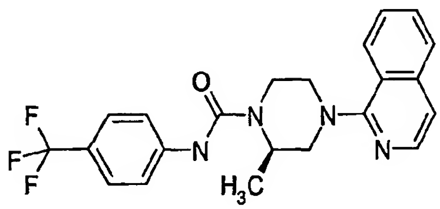
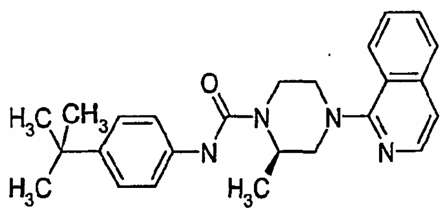
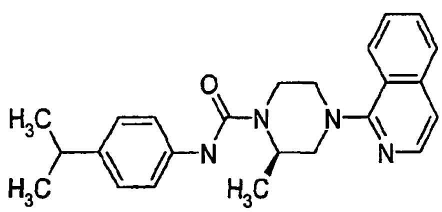
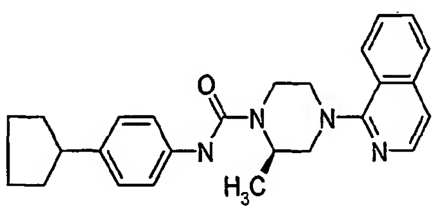
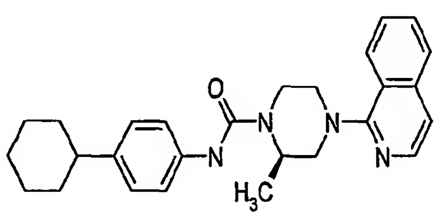
8	4-Isopropyl	H	H	NH	3-Cl	359	359, 381 Na adduct	*	4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide
9	4-Isopropyl	H	H	NH	3,5-diCl	393	393, 415 Na adduct	*	4-(3,5-Dichloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide
10	4-Isopropyl	H	H	CH=CH	3-CF3			*	1-(3-Methyl-2-pyridinyl)-3-(4-trifluoromethyl phenyl)-prop-2-en-1-one
11	4-CF3	H	H	CH=CH	3-Me			*	1-(3-Trifluoromethyl-2-pyrindinyl)-3-(4-isopropylphenyl)-prop-2-en-1-one
12	4-Isopropyl	H	H	NH	3-CN	349		*	4-(3-Cyano-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide
13	4-Isopropyl	Me	H	NH	3-Cl	373	373, 395 Na adduct	NA	4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-2-methyl-1-piperazinecarboxamide
14	4-Isopropyl	R-Me	H	NH	3-Cl	373	373, 395 Na adduct	*	4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide
15	4-Isopropyl	S-Me	H	NH	3-Cl	373	373, 395 Na adduct	NA	4-(3-Chloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-2-methylthio-1-piperazinecarboxamide
16	4-CF3	H	H	NH	3,5-diCl	373		NA	4-(3,5-Dichloro-2-pyridinyl)-N-[4-(isopropyl)phenyl]-1-piperazinecarboxamide

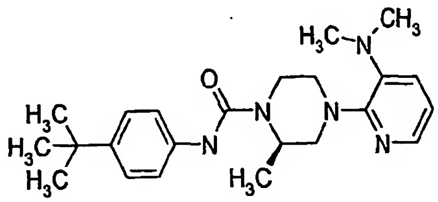
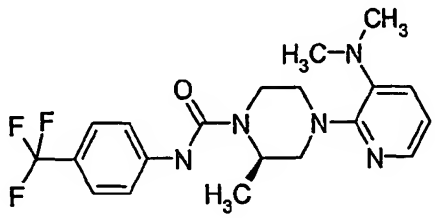
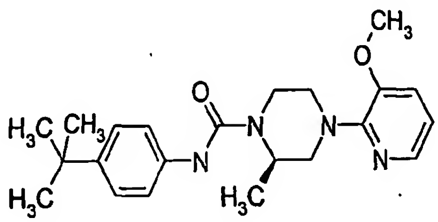
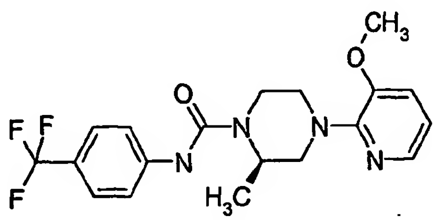
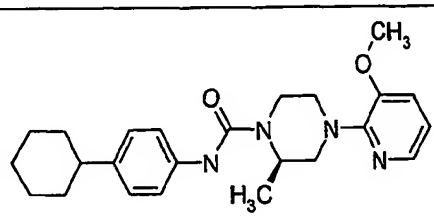
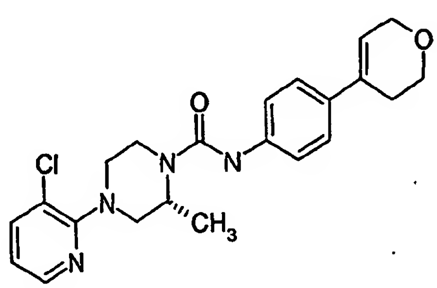
* indicates a Ki value of less than 4 uM in a Capsaicin receptor binding assay A Capsaicin receptor binding assay is described in example 10 NA = Not available
Mass spec data are collected using a MicroMass 60 series (Beverly, MA) LC-MS TOF spectrometer in the electrospray mode. LC conditions: YMC-pack pro C18 column, 33 x 4.6 ID, Particle size: S-5 µm 120A, supplied by WATERS, Milford, MA, 95%- 5% gradient, 2 min gradient time, flow rate 3.5 ml/min, Mobile Phase:A: 0.05% TFA in H2O/MeOH (95:5 v/v)B: 0.05% TFA IN MeOH/H2O(95:5 v/v), 1 ul injection volume .

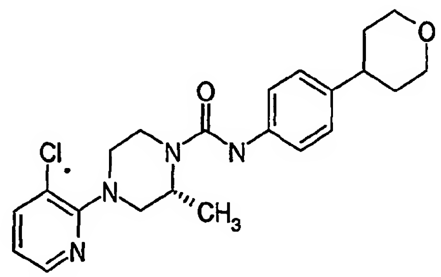
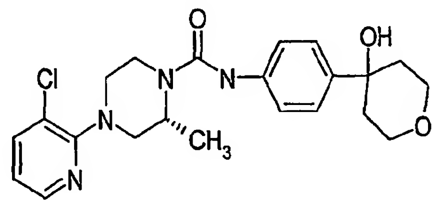
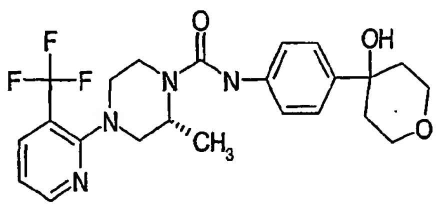
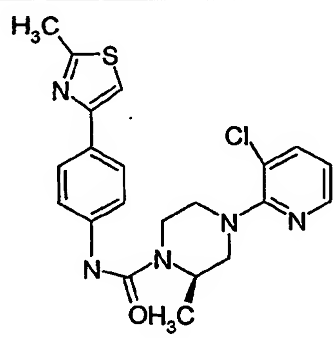
Table III			
Cmp. #	STRUCTURE	IUPAC Name	EC50
17		N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide	*
18		(2R)-4-(3-chloropyridin-2-yl)-N-(4-cyclohexylphenyl)-2-methylpiperazine-1-carboxamide	*
19		(2R)-4-(3-chloropyridin-2-yl)-N-[2-chloro-4-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxamide	
20		(2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
21		(2R)-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
22	 Chiral	(2R)-4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide	*
23	 Chiral	(2S)-4-(3-chloropyridin-2-yl)-N-(4-trifluoromethylphenyl)-2-methylpiperazine-1-carboxamide	*

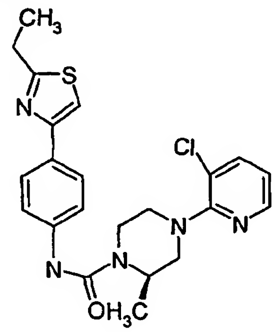
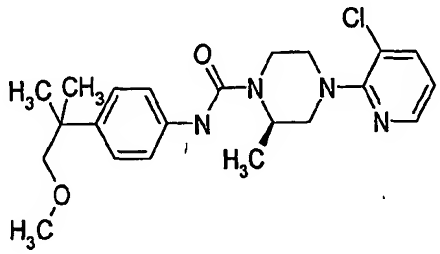
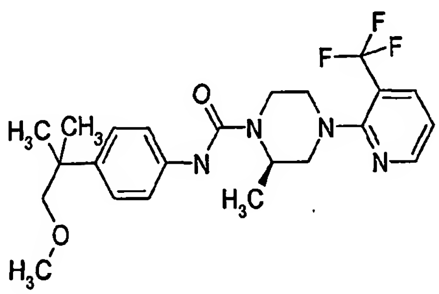
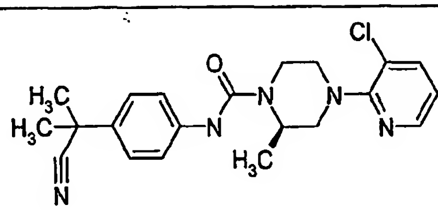
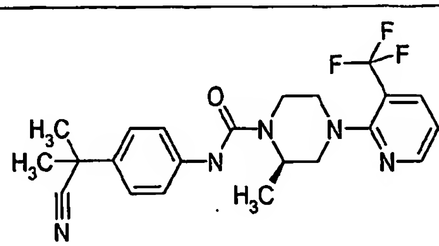
24		(2S)-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
25		(2S)-4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide	*
26		(2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(4-piperidin-1-ylphenyl)piperazine-1-carboxamide	*
27		(2R)-4-(3-chloropyridin-2-yl)-N-[2-fluoro-4-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxamide	*
28		(2R)-2-methyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
29		(2R)-N-(4-tert-butylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*

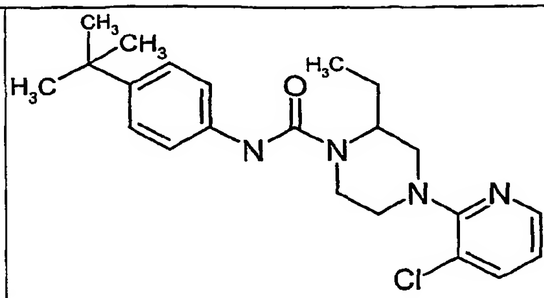
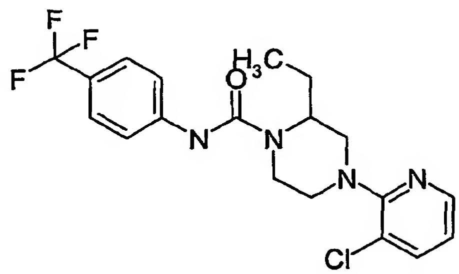
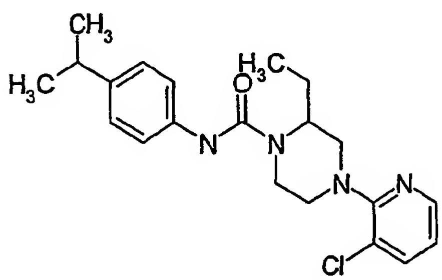
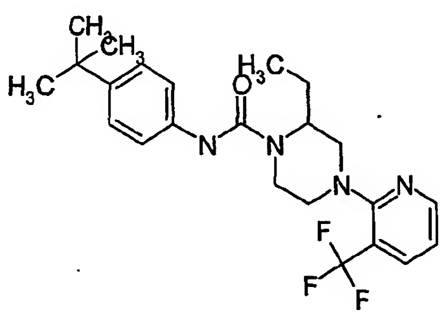
30		(2R)-N-(4-isopropylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
31		4-(3-chloropyridin-2-yl)-2,6-dimethyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
32		N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	*
33		4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)-2,6-dimethylpiperazine-1-carboxamide	*
34		(2R)-N-(4-cyclohexylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
35		4-(3-chloropyridin-2-yl)-N-(4-cyclohexylphenyl)-2,6-dimethylpiperazine-1-carboxamide	*
36		(2R)-4-(3-chloropyridin-2-yl)-N-(4-cyclopentylphenyl)-2-methylpiperazine-1-carboxamide	*

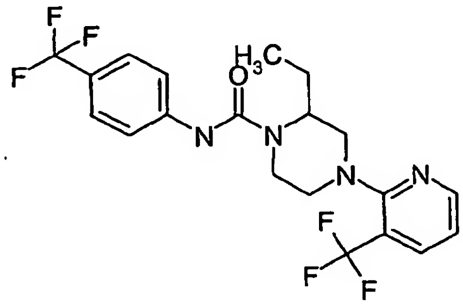
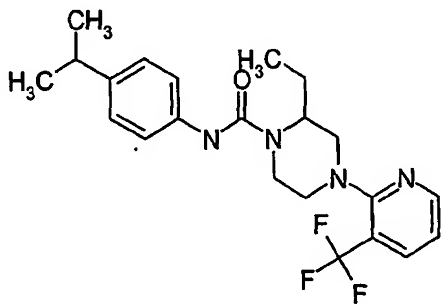
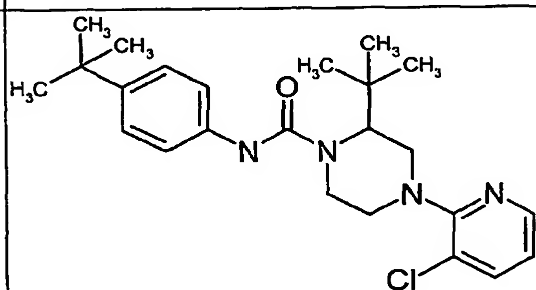
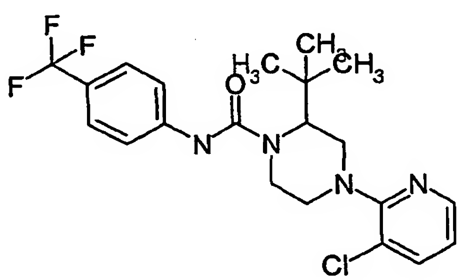
37		(2R)-N-(4-cyclopentylphenyl)-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
38		(2R)-4-isoquinolin-1-yl-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
39		(2R)-N-(4-tert-butylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide	*
40		(2R)-N-(4-isopropylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide	*
41		(2R)-N-(4-cyclopentylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide	*
42		(2R)-N-(4-cyclohexylphenyl)-4-isoquinolin-1-yl-2-methylpiperazine-1-carboxamide	*

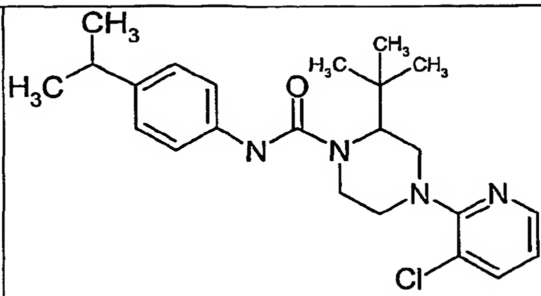
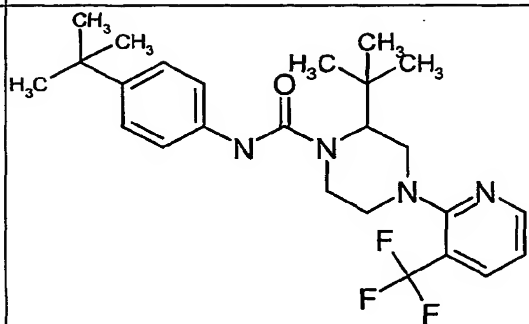
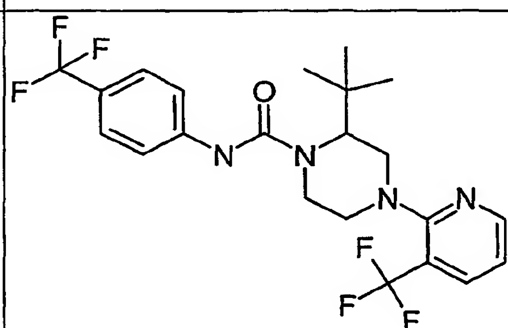
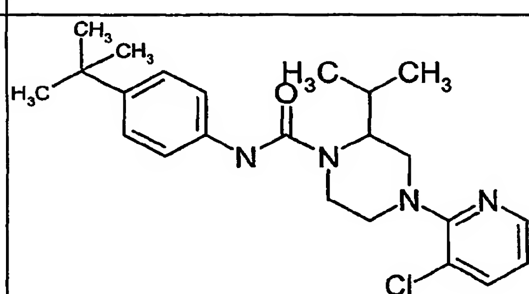
43		(2R)-N-(4-tert-butylphenyl)-4-[3-(dimethylamino)pyridin-2-yl]-2-methylpiperazine-1-carboxamide	*
44		(2R)-4-[3-(dimethylamino)pyridin-2-yl]-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
45		(2R)-N-(4-tert-butylphenyl)-4-(3-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
46		(2R)-4-(3-methoxypyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	
47		(2R)-N-(4-cyclohexylphenyl)-4-(3-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
48		(2R)-4-(3-chloropyridin-2-yl)-N-[4-(3,6-dihydro-2H-pyran-4-yl)phenyl]-2-methylpiperazine-1-carboxamide	*

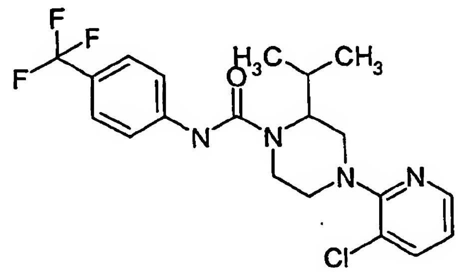
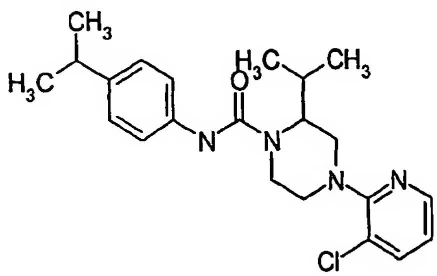
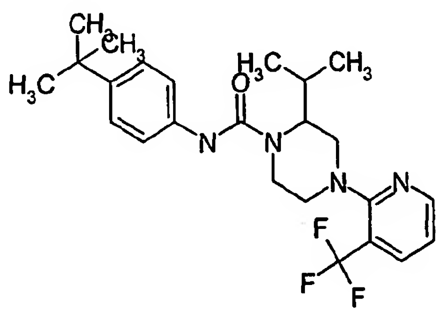
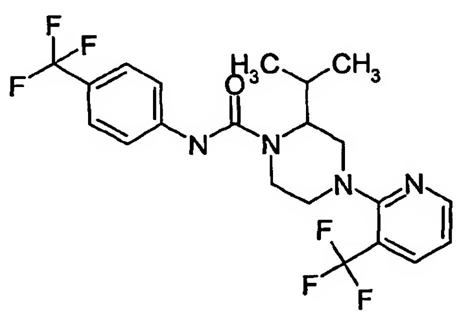
49		(2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-(4-tetrahydro-2H-pyran-4-ylphenyl)piperazine-1-carboxamide	*
50		(2R)-4-(3-chloropyridin-2-yl)-N-[4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl]-2-methylpiperazine-1-carboxamide	*
51		(2R)-N-[4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl]-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
52		(2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[4-(2-methyl-1,3-thiazol-4-yl)phenyl]piperazine-1-carboxamide	*

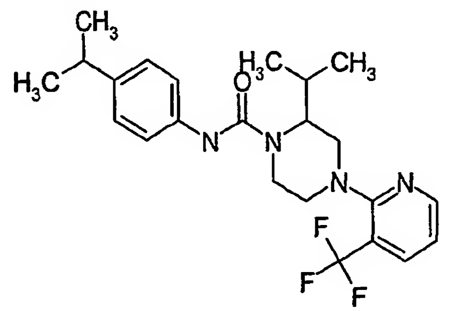
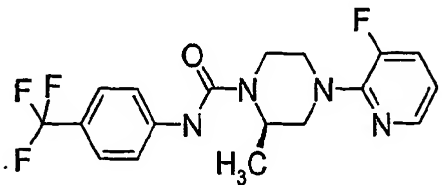
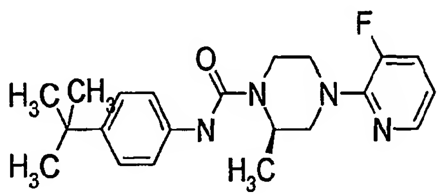
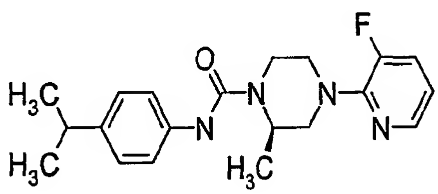
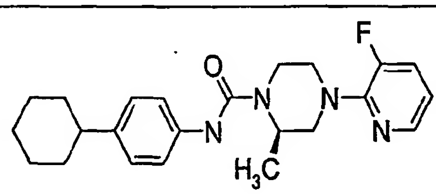
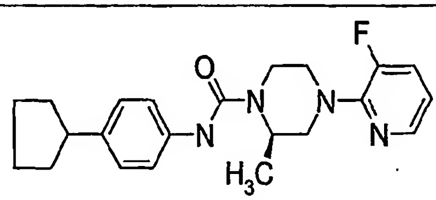
53		(2R)-4-(3-chloropyridin-2-yl)-N-[4-(2-ethyl-1,3-thiazol-4-yl)phenyl]-2-methylpiperazine-1-carboxamide	*
54		(2R)-4-(3-chloropyridin-2-yl)-N-[4-(2-methoxy-1,1-dimethylethyl)phenyl]-2-methylpiperazine-1-carboxamide	*
55		(2R)-N-[4-(2-methoxy-1,1-dimethylethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
56		(2R)-4-(3-chloropyridin-2-yl)-N-[4-(1-cyano-1-methylethyl)phenyl]-2-methylpiperazine-1-carboxamide	*
57		(2R)-N-[4-(1-cyano-1-methylethyl)phenyl]-2-methyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*

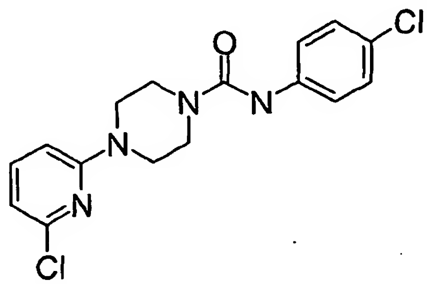
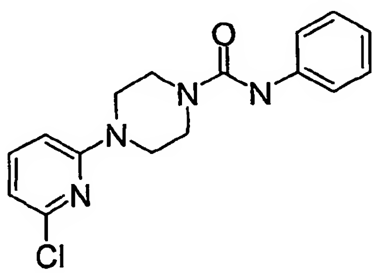
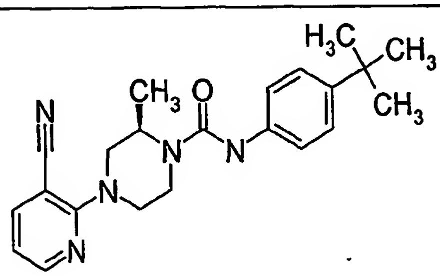
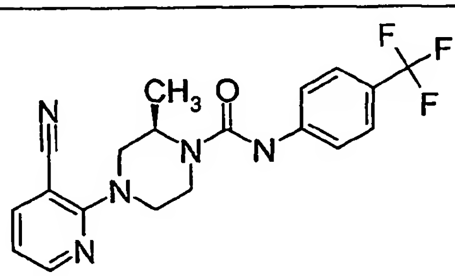
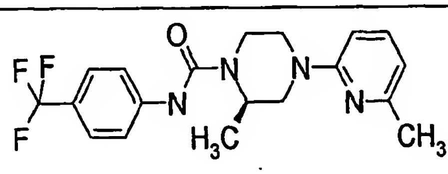
58		N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-ethylpiperazine-1-carboxamide	*
59		4-(3-chloropyridin-2-yl)-2-ethyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
60		4-(3-chloropyridin-2-yl)-2-ethyl-N-(4-isopropylphenyl)piperazine-1-carboxamide	*
61		N-(4-tert-butylphenyl)-2-ethyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*

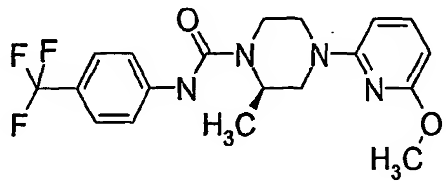
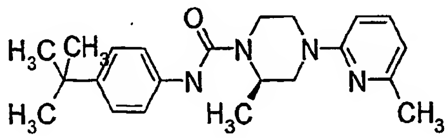
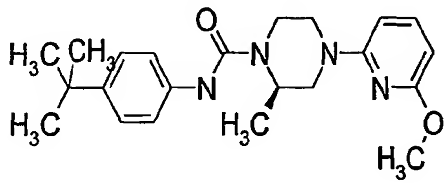
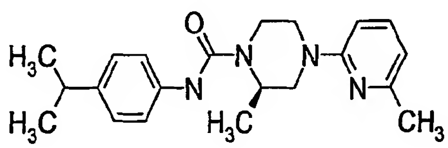
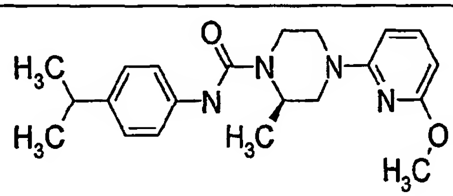
62		2-ethyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
63		2-ethyl-N-(4-isopropylphenyl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
64		2-tert-butyl-N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide	*
65		2-tert-butyl-4-(3-chloropyridin-2-yl)-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	

66		2-tert-butyl-4-(3-chloropyridin-2-yl)-N-(4-isopropylphenyl)piperazine-1-carboxamide	
67		2-tert-butyl-N-(4-tert-butylphenyl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	
68		2-tert-butyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
69		N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl)-2-isopropylpiperazine-1-carboxamide	*

70		4-(3-chloropyridin-2-yl)-2-isopropyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	
71		4-(3-chloropyridin-2-yl)-2-isopropyl-N-(4-isopropylphenyl)piperazine-1-carboxamide	
72		N-(4-tert-butylphenyl)-2-isopropyl-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
73		2-isopropyl-N-[4-(trifluoromethyl)phenyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*

74		2-isopropyl-N-(4-isopropylphenyl)-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
75		(2R)-4-(3-fluoropyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
76		(2R)-N-(4-tert-butylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
77		(2R)-4-(3-fluoropyridin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide	*
78		(2R)-N-(4-cyclohexylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
79		(2R)-N-(4-cyclopentylphenyl)-4-(3-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide	*

80		N-(4-chlorophenyl)-4-(6-chloropyridin-2-yl)piperazine-1-carboxamide	
81		4-(6-chloropyridin-2-yl)-N-phenylpiperazine-1-carboxamide	
82		(2R)-N-(4-tert-butylphenyl)-4-(3-cyanopyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
83		(2R)-4-(3-cyanopyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
84		(2R)-2-methyl-4-(6-methylpyridin-2-yl)-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	

85		(2R)-4-(6-methoxypyridin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	
86		(2R)-N-(4-tert-butylphenyl)-2-methyl-4-(6-methylpyridin-2-yl)piperazine-1-carboxamide	*
87		(2R)-N-(4-tert-butylphenyl)-4-(6-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide	
88		(2R)-N-(4-isopropylphenyl)-2-methyl-4-(6-methylpyridin-2-yl)piperazine-1-carboxamide	
89		(2R)-N-(4-isopropylphenyl)-4-(6-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide	

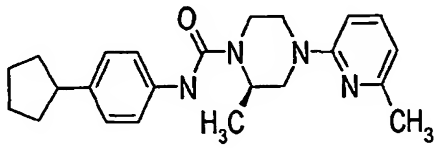
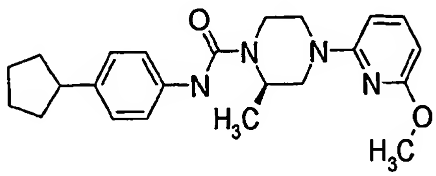
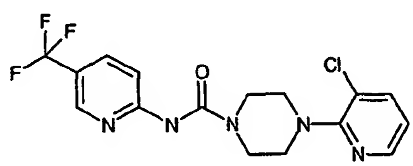
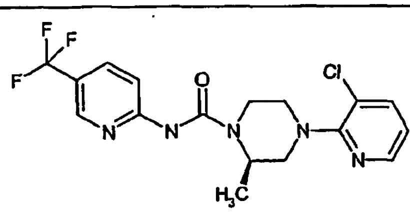
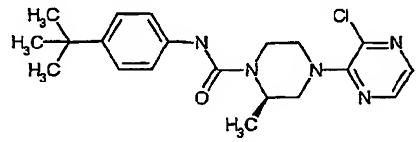
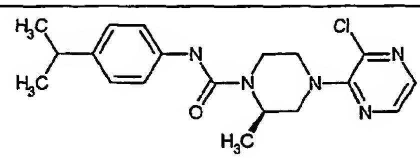
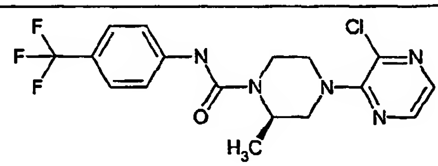
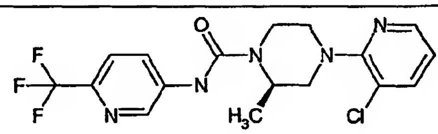
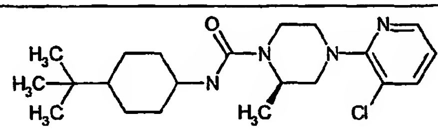
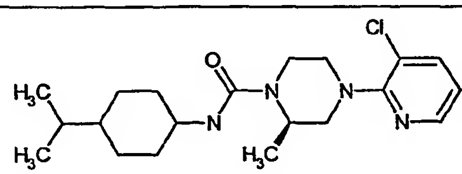
90		(2R)-N-(4-cyclopentylphenyl)-2-methyl-4-(6-methylpyridin-2-yl)piperazine-1-carboxamide	
91		(2R)-N-(4-cyclopentylphenyl)-4-(6-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide	

TABLE IV			
Cpd. #	STRUCTURE	IUPAC Name	EC50
93		4-(3-chloropyridin-2-yl)-N-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*
94		(2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	*

95		(2R)-N-(4-tert-butylphenyl)-4-(3-chloropyrazin-2-yl)-2-methylpiperazine-1-carboxamide	*
96		(2R)-4-(3-chloropyrazin-2-yl)-N-(4-isopropylphenyl)-2-methylpiperazine-1-carboxamide	*
97		(2R)-4-(3-chloropyrazin-2-yl)-2-methyl-N-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	*
98		(2R)-4-(3-chloropyridin-2-yl)-2-methyl-N-[6-(trifluoromethyl)pyridin-3-yl]piperazine-1-carboxamide	*
99		(2R)-N-(4-tert-butylcyclohexyl)-4-(3-chloropyridin-2-yl)-2-methylpiperazine-1-carboxamide	*
100		(2R)-4-(3-chloropyridin-2-yl)-N-(4-isopropylcyclohexyl)-2-methylpiperazine-1-carboxamide	*